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In the short space of four years synthetic detergents have made a tremendous change in the household washing habits of American housewives. At the start of 1948 they accounted for less than 10% of the "laundry soap" business; by the end of 1951 they accounted for over 60%. The product enjoying the greatest popularity in this classification (Tide) is currently being used by one woman out of every four who do their own dishes, and one out of every three who do their own laundry.

For your information the Chemical Division of The Procter & Gamble Company has prepared this article, discussing some of the differences between synthetics and soaps which formerly were widely used for household washing.

How synthetic detergents differ from soaps

Synthetic detergents are organic compounds with molecules whose opposite ends are highly polarized like those of soap; one end consists of the type of structure which is oil soluble, the other consists of the type which is water soluble.

Magnesium and calcium soaps formed by interaction of sodium soaps with water hardness are among the most insoluble of compounds. The precipitation which occurs with soap in hard water wastes soap and causes cloudy glassware and unsightly deposits. The "tailor-made" molecules of synthetics do not form these insoluble compounds in hard water. They, therefore, leave surfaces cleaner because they are free of any precipitated "soap film" formed during rinsing. Also, unlike soaps, in solution, synthetics can be used at almost any pH. Soaps, of course, must be kept at pH 10 or above, or they will split into fatty acids. Most synthetic products in general use have solution pHs from 6.0—10.0. Few are above the pH of soap.

The special washing abilities of synthetic detergents

As a consequence of the characteristics discussed above, synthetics are particularly well-suited for washing off acidic soils which would destroy soap. Since they aren't destroyed by hardness or by salts of other metals as soaps are, they are well-suited to washing a great variety of things which could be washed only with alkalis before—for instance, glass laboratory utensils.

The effect of synthetic detergents on bacteria

The synthetics in general and widespread use have about the same general effect on bacteria as soaps —that is, they have some germicidal effect on some strains, but for creating relatively sterile conditions, synthetic detergents rely more on removing bacteria than on killing them.

Detergents

The effect of synthetic detergents on skin

Over the past seven years Procter & Gamble has included these synthetic detergents in the continuing series of tests, designed to measure the effect of washing products on skin. In addition to the routine patch and arm-immersion tests, Procter & Gamble has conducted, under careful medical supervision, extensive clinical and home-usage tests of all its products, including the new synthetic detergents. These tests indicate that household detergents in use today, as a class, do not differ greatly in their effect on the skin from the general-purpose package soaps which have been used for years. Some have a lower pH than soaps and, hence, less effect on persons sensitive to alkali.

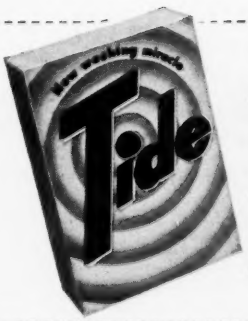
Like soaps, the detergents generally are mild primary irritants, but a fact not generally realized is that on the average person subjected to patch tests or immersion tests, most detergent solutions cause less skin reaction than do soap solutions.

Women have had many years in which to learn whether or not all soaps or certain soaps prove irritating in each particular case. Any problems arising from the effect of soap on skin have, therefore, been spread over decades. In the case of washday detergents, practically every woman in America was exposed to these products in a concentrated period of two or three years.

This great popularity and widespread use of synthetic detergents, together with their relative newness on the market, have resulted in a situation where synthetic detergents are likely to be suspected as the cause of many cases of dermatitis where they probably are not involved at all. With almost all housewives now using synthetic detergents for one or more purposes in their homes, it is inevitable that when a physician sees a case of hand dermatitis, a history of exposure to detergents will be obtainable. The significance of the dermatitis must be appraised against the background of the wide use of the detergent products.

For further information . . .

send for free booklet, "About Synthetic Detergents—Facts for Physicians." Write: The Procter & Gamble Co., Box 687B, Cincinnati 2, Ohio.



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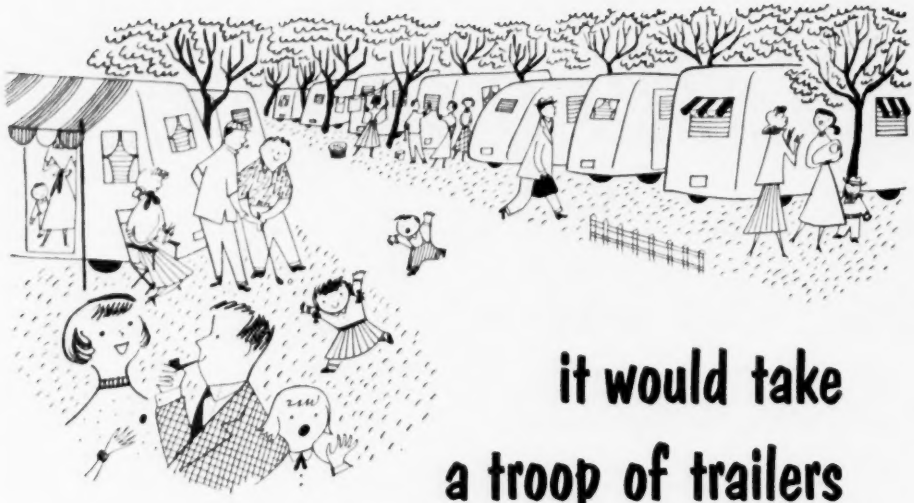

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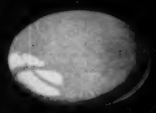

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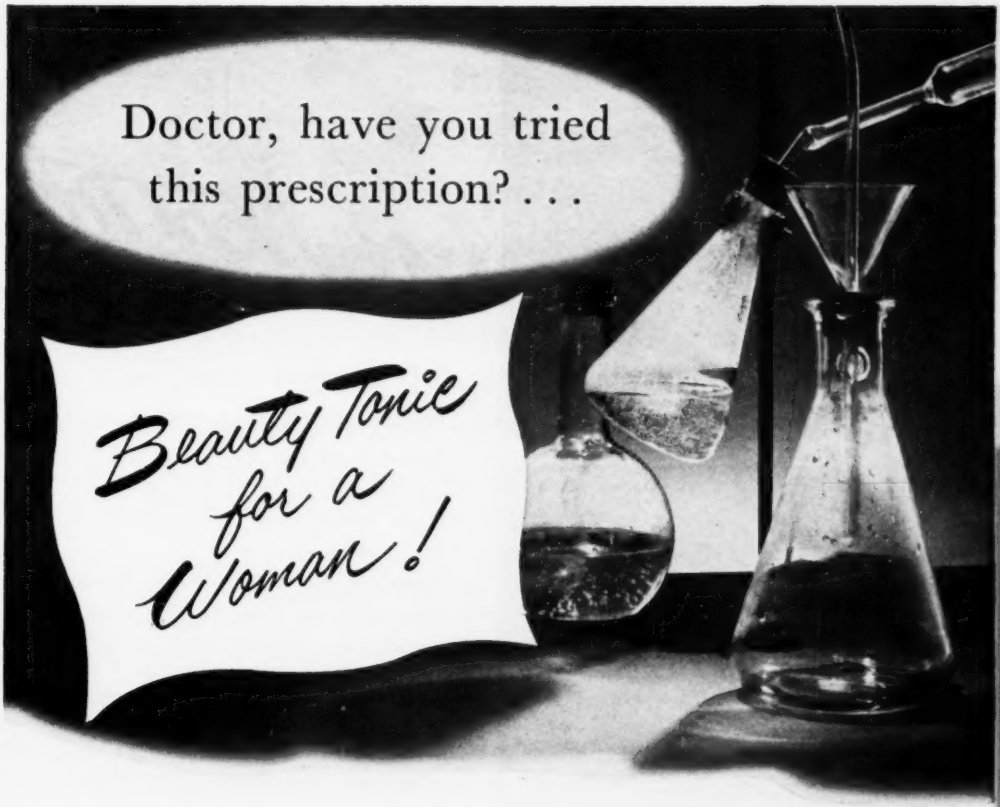

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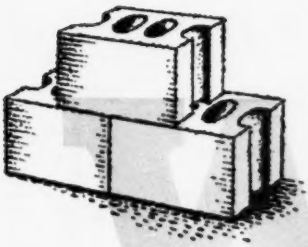

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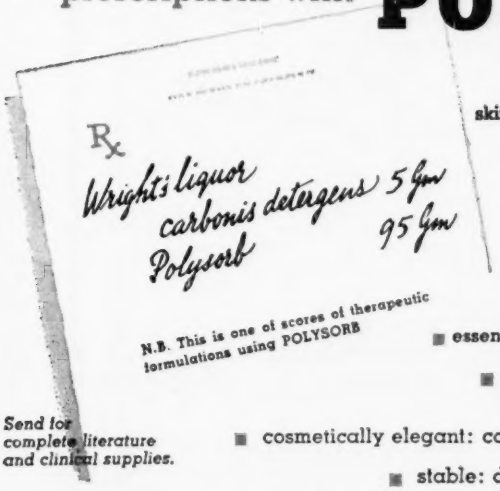
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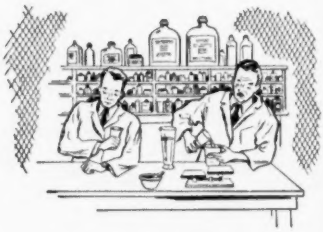

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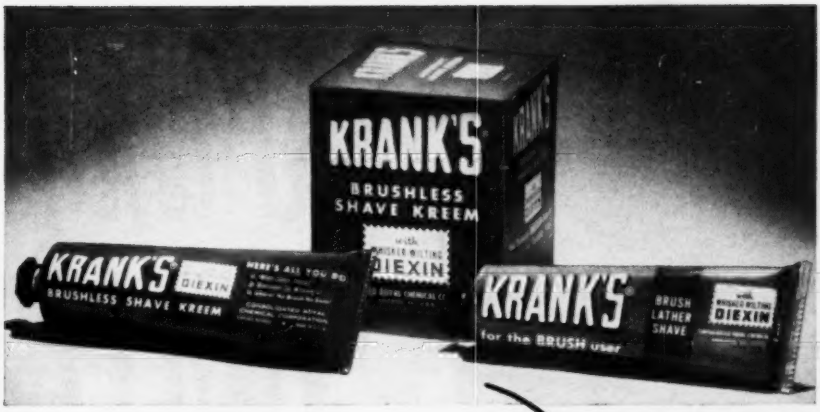

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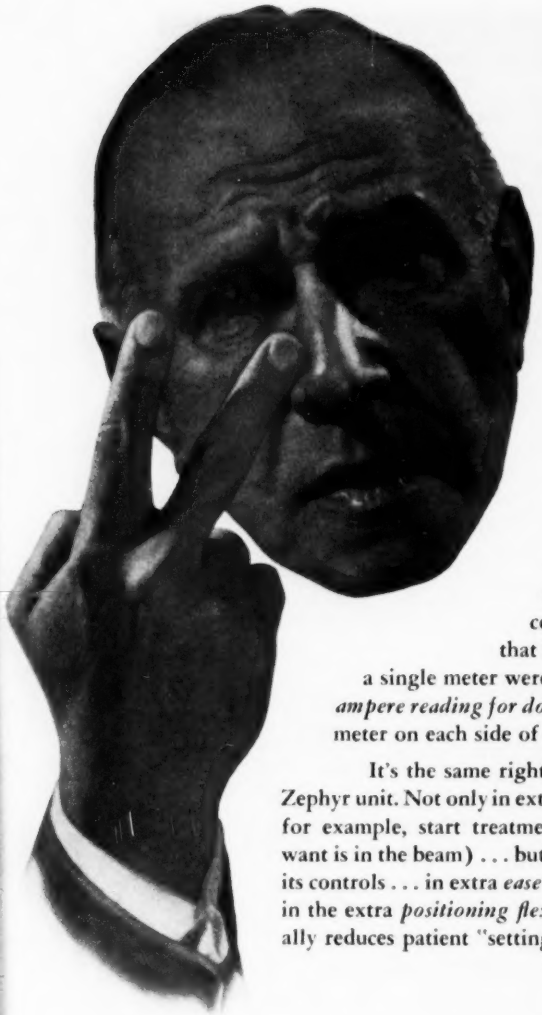

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Archives of Dermatology and Syphilology

VOLUME 66 SEPTEMBER 1952 NUMBER 3

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DERMATOLOGY AT THE CROSSROADS

Presidential Address

EDWARD A. OLIVER, M.D.
CHICAGO

IN A PAPER recently published by Senear, Lewis, and Cormia, the statement was made that dermatology was at the crossroads; that it, in common with other medical specialties, had progressed a long way, but that it could not remain static, that its future must be one of expansion.

I am in full accord with this statement; but I believe that with the type of men we now have in our specialty, we are bound to travel the right road. I am well aware that for some time past there has been a concerted but shortsighted effort on the part of some medical schools to make dermatology a very minor specialty. To overcome this trend, we must be alert. We cannot afford to cease fighting for what we believe is our rightful place, else we shall lose our identity as a specialty.

During my lifetime I have seen many advances made in dermatology. I, of course, realize our shortcomings.

I should like first to cite some examples of our progress. Later on, I shall consider some of our deficiencies.

The Chicago Dermatological Society has afforded me the opportunity of witnessing the growth of dermatology in Chicago. When I first began to attend meetings as a guest back in 1912, the meeting place was Dr. Ormsby's office, occasionally Dr. Pusey's. About a dozen men were usually present at these meetings, which were held once a month. Ten to 15 interesting cases were shown; the discussions were lively, sometimes quite animated, and were very instructive to me, but, as I look back, it seems that the cases lacked the careful preparation that they show today. Seldom were histopathological slides shown. The discussions were purely on a clinical basis.

Our society has grown rapidly. We have been compelled to move at least five different times to accommodate our increased attendance. Now our meetings are held in a large room at the University of Illinois Union. The cases are displayed both at the University of Illinois and at the Cook County Hospital. An average of 35 to 45 cases is shown at these meetings, and those attending will vary from 100 to 130, of whom 55 are members of our society.

The cases are all well presented with complete histories, microscopic slides, blood cell counts, and blood chemistry examinations, when these are necessary. Our meetings are much more scientific, and the knowledge of histopathology, allergy, and biochemistry displayed by our younger members is most gratifying.

Read at the Seventy-Second Annual Meeting of the American Dermatological Association, Colorado Springs, Colo., April 23, 1952.

This same thing is occurring in cities all over the country. In 1912 we had only a few dermatological societies. Now we have 10 sectional societies, 15 state societies, and 23 local societies. In 1912 our national organizations consisted only of this one, the American Dermatological Association, and the Section on Dermatology of the American Medical Association. In his presidential address in 1922, Ormsby stated that there were approximately 300 physicians practicing dermatology and syphilology in the United States. In 1939 Senear reported 866 physicians limiting their practice to dermatology and syphilology and 415 who indicated a special interest in the subject. Today we have 1,361 diplomates certified by the American Board of Dermatology and Syphilology.

Our two relatively new organizations, the American Academy of Dermatology and Syphilology and the Society for Investigative Dermatology, have done much to stimulate American dermatology.

I know of no one incident that has done more for American dermatology than the founding of the academy. Four of the members of this Association are responsible for its birth, Dr. Paul O'Leary, Dr. Charles Dennie, Dr. Harry Foerster, and Dr. Earl Osborne. Its growth has been startling. At our last meeting in December, 1951, more than 1,000 dermatologists were in attendance. The program was most instructive, and dermatologists from far and near were enthusiastic in their praise of this educational institution.

To those of the medical profession who are inclined to view us as externists, I suggest a glance at our 1951 program. Surely no other medical organization can boast of a better, more scientific group of symposia, lectures, and courses than this annual program offers.

Too much credit cannot be given those men who are so generous with their time and ability in teaching the courses on histopathology, mycology, x-ray and radium therapy, and other subjects.

Another society which does great credit to American dermatology is the Society for Investigative Dermatology. This institution fills a long-felt need in that it affords to those who are carrying on investigative work an opportunity for reporting the results of their studies before an interested audience at the annual meeting. *The Journal of Investigative Dermatology* offers them a medium for the the publication of their papers. The annual meetings are well attended, and the papers presented are a credit to investigative dermatology. This society deserves especial commendation for stimulating young men to do both clinical and laboratory investigation.

I would be remiss if I did not mention as a sign of our progress our two splendid monthly publications, the A. M. A. ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY and *The Journal of Investigative Dermatology*. Both of them rank high among the medical periodicals published not only in this country but throughout the world.

The growth of dermatology has been most encouraging. The rapidity of its growth was stimulated by the second World War, especially the war in the South Pacific, where cutaneous diseases were very prevalent. Many young officers of the Army and Navy confronted with difficult dermatological cases realized the importance of this branch of medicine and came home with a desire to make the practice of dermatology their lifework. For a short time our available resources for training these men were not adequate, but eventually we were able to accommodate them. Our graduate training program has expanded greatly. In 1940 there were only 20

institutions approved for graduate training in dermatology and syphilology; today there are 80 approved institutions, some for the full three years, some for two, and a few for one year.

Because of the large number of young men finishing training in the last three or four years, the American Board of Dermatology has had a great deal of work to do. It has done a splendid service for dermatology, and to its present and former members who have spent many hours of hard work in orally examining candidates, grading papers, and preparing examinations, we owe a debt of gratitude.

Unfortunately, the board has no voice in advising these young diplomates where to locate; otherwise the distribution of dermatologists throughout the country might be different. Too many of the younger men are locating in the large cities. It can readily be understood why the young dermatologist about to begin practice prefers to locate in the larger cities. A position on the teaching staff of a medical school, an affiliation with a good hospital, the opportunity to attend dermatological society meetings, and the proximity of medical libraries are excellent reasons for his remaining in the city. I believe, however, that we, as older men and preceptors, should advise these young diplomates of the opportunities awaiting them in the smaller and medium-sized cities. There is need for good men in these localities.

Thus far, I have stressed our accomplishments and our progress; now I should like to mention some of our weaknesses.

Our graduate teaching program is working out well, but our teaching of dermatology to undergraduate students is and has been woefully inadequate. How much of this is our fault, I do not know. I realize that, owing to the increasing amount of time demanded by the departments of medicine and surgery in most medical schools, little time is left for the teaching of the specialties, especially dermatology, despite the fact that statistics show that 12 to 15% of all patients the general practitioner sees in his office are dermatological patients. Many medical school curricula are about as full as they can be, and the excellent recommendations made by the Committee on Education of this Association, of which Dr. C. Guy Lane is chairman, may fall on deaf ears unless the chairman of the department has a strong enough personality and enough persuasive ability to influence the dean and his faculty to allot him sufficient time to present this subject adequately.

Interest in dermatology for the average medical student depends upon the ability of the teaching staff to present it in a convincing manner. Dermatology can be made one of the most popular and interesting courses in the medical curriculum, provided that the chairman of the department and his associates have sufficient teaching material and approach their work with enthusiasm. The serious-minded medical student appreciates good clinics and good teaching.

I recall vividly my medical student days, and especially my clinical years at Rush Medical College. The first worth-while advice I received from the all-wise seniors was to be sure to enroll in Dr. Ormsby's clinic at the Cook County Hospital. This clinic was one of the most popular given at Rush. It was always crowded and attracted not only the students who had registered for it but many visitors besides. This was because Dr. Ormsby had a wealth of material to draw from and he presented his cases well. In other words, he knew his subject. It did not require any compulsion to make a student register for his course. In fact, many students deliberately "cut" other clinics to attend his. Dermatology was always one of the most popular courses given at Rush Medical College.

I mention this to emphasize again the importance of good teaching. It is in this way that we shall attract alert, brilliant young men to enter the field of dermatology. You, as chairmen and members of your respective departments, can do much to make dermatology popular.

Investigation and research require hospital beds for the study of both common and unusual cases, and this is one of our greatest needs. It is commendable and surprising that dermatology has made the strides it has with as few hospital beds as there have been at our disposal.

It is true that large institutions, such as the Mayo Clinic, the Universities of Michigan, Chicago, and Iowa, and the Barnard Free Skin and Cancer Hospital, have adequate facilities and hospital beds for the study of cutaneous diseases, but in many cities such facilities are very inadequate. One of the first things a European dermatologist notices when he visits Chicago is our scarcity of hospital beds for dermatological patients. This is surprising to him, in view of the fact that nearly every city of any size in Europe has either a wing in a large general hospital set aside for skin diseases or a dermatological institute.

This problem is an important one, and we should keep it continually before us.

We have several other problems confronting us, but fortunately syphilis is not one of them. Little did I believe even as recently as fifteen years ago that we would see the day when we would not have cases of cutaneous syphilis to show in our clinics. What the recent advances in therapy have done in eradicating this disease is simply amazing.

I recently received the report of the Health Department of the City of Chicago for 1951. This report includes all cases reported by the Intensive Treatment Center, a clinic conducted by the Health Department of the city, the Cook County Hospital, the various medical school clinics, and private physicians. In 1946, there were 16,190 cases of syphilis reported, of which 4,322 were of primary and secondary syphilis and 4,767 were of early latent syphilis. In 1951, a short space of five years, there was an astounding drop—only 5,128 cases of syphilis of all types were reported, 477 of these were of primary and secondary syphilis and 1,995 were of early latent syphilis.

The authorities could not give me the exact figures, but they did tell me that they had noted a great many cases of reinfection; in fact, they cited three reinfections in one man in one year.

Despite the fact that we are seeing relatively little active syphilis in clinics and practically none in private practice, I still feel that we should continue to teach syphilis to both graduate and undergraduate students, if not with actual cases of the disease then with lantern slides and lectures.

In view of our experience with syphilis, and we must admit that it has now become a public health problem, we should be concerned with the growing tendency to centralize the treatment of cancer of all kinds in cancer institutes and cancer clinics. I am very much in favor of the intensive drive against cancer that is sweeping the country, but I am, and I know you are, of the opinion that treatment of cancer of the skin belongs to the dermatologist. We are thoroughly capable of treating at least 95% of such cancers. The other 5% may be handled by the plastic surgeon or the chemosurgeon, not by the radiologist. Unless we are alert and publicize the fact that cancer of the skin can be and should be treated by the der-

matologist, we are apt in the near future to see these institutes and cancer clinics take over the treatment of cutaneous cancer. Many of them are doing this now.

We can counteract this trend by reading papers on cancer before our local societies, by publishing articles in our state journals, and by giving the subject of cancer of the skin more attention in the sectional meetings of the American Medical Association and our academy meetings.

Our undergraduate and graduate students should be taught to recognize cancer in its early stages, melanomas and the so-called precancerous dermatoses. They should also be taught the importance of taking biopsy specimens and the most modern methods of treatment.

Another field we have neglected is that of the industrial dermatoses. More papers should be written and more talks given by the dermatologist on the various dermatoses common in industry. We have an annual symposium on industrial dermatoses at our academy meeting, but it might be advantageous to us to allot time for one or two papers on this important subject at our American Medical Association meetings and at the meetings of this Association.

In view of our recently acquired knowledge of lupus erythematosus and sarcoidosis, it would seem that a closer association with internal medicine is most necessary. It is unfortunately true that we know little more about the etiology of a number of common dermatoses, such as psoriasis, lichen planus, dermatitis herpetiformis, and pemphigus, than we did years ago. Investigators should find some of these dermatoses a fruitful field.

I am convinced that our ever-increasing knowledge of hematology, virology, allergy, physiology, and biochemistry may lead us to the solution of some of these problems.

It is essential that we attract to our specialty young men who have this knowledge and who have a desire to investigate.

If this can be accomplished, we shall continue to progress and our future will be secure.

LOCAL ACTION OF STEROIDS ON SENILE HUMAN SKIN

JOSEPH W. GOLDZIEHER, M.D.
IRENE S. ROBERTS, Ph.D.
WILLIAM B. RAWLS, M.D.
AND
MAX A. GOLDZIEHER, M.D.
NEW YORK

CONSIDERABLE evidence has accumulated showing that steroids applied locally have a profound effect upon the skin and its accessory structures. As early as 1929, Loeb and Haven [1] showed that injection of estrogen into ovariectomized adult guinea pigs accelerated mitosis and proliferation and increased the cell population of the epidermis. In 1937, Kun [2] demonstrated that the same changes could be induced in infantile or senile rats (i. e., rats with low estrogen production) by the topical administration of estradiol in an ointment. In the skin of the mouse cyclic changes synchronous with the estrous cycle were described by Bullougii [3] in 1943; maximal activity of the epidermal cells was correlated with the high-estrogen phase of the cycle or could be produced artificially during diestrus by estrogen injections. Recent studies [4] by means of skin spectrophotometry have demonstrated cutaneous vascular changes in women correlated with fluctuations in estrogen levels; this confirmed the observation of dermovascular reactions consequent to the administration of testosterone or estrogen.[5] Selye [6] reported a marked increase in the keratinized epidermis of genetically hairless mice following topical administration of estradiol in oil. Hooker and Pfeiffer [7] in 1943 showed that large doses of estrogen (166 γ per week subcutaneously) produced definite thinning of the epi-

From the Research Department, St. Clare's Hospital.

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1. Loeb, L., and Haven, F. L.: The Relation Between Functional States of the Sex Organs in the Female Guinea Pig and the Cell Proliferation in the Epidermis, Anat. Rec. **43**:1-26, 1929.

2. Kun, H.: The Effect of the Follicle Hormone on the Skin Through Local Application: Histologic Studies in Infantile and Senile Rats, Wien. klin. Wchnschr. **50**:408-411, 1937.

3. Bullough, H. F.: Cyclical Changes in the Skin of the Mouse During the Estrous Cycle, J. Endocrinol. **3**:280-287, 1943.

4. Edwards, E. A., and Duntley, S. Q.: Cutaneous Vascular Changes in Women in Reference to the Menstrual Cycle and Ovariectomy, Am. J. Obst. & Gynec. **57**:501-509, 1949.

5. Reynolds, S. R. M.; Hamilton, J. B.; DiPalma, J. R.; Hubert, G. R., and Foster, F. I.: Dermovascular Actions of Certain Steroid Hormones in Castrate, Normal and Eunuchoid Men, J. Clin. Endocrinol. **2**:228-236, 1942.

6. Selye, H.: Effect of Estradiol Locally Applied to Abnormal Skin, Arch. Dermat. & Syph. **50**:261-263, 1944.

7. Hooker, C. W., and Pfeiffer, C. A.: Effects of Sex Hormones upon Body Growth, Skin, Hair and Sebaceous Glands in the Rat, Endocrinology **32**:69-76, 1943.

dermis within 2 months; this became pronounced in 10 months. These workers went further to show that two injections totaling 5 mg. of testosterone propionate per week induced epidermal proliferation in the rat; simultaneous administration of estrogen and testosterone produced no thinning. Estrogen was found to cause atrophy of the sebaceous glands and inhibition of hair growth; estrogen plus testosterone was found to have no effect on the sebaceous glands. Recent studies by Dunaif and Finerty [8] on prepuberally ovariectomized young rats have confirmed the finding that small doses of estradiol benzoate, given either topically or by injection, increased epidermal mitosis and cell population counts. (Similar observations have also been made by Bullough.[9]) The rate of mitosis, decreased in the young rats by ovariectomy, was restored to normal by estrogen. On the other hand, large doses (5 γ subcutaneously or 15 γ topically) of estradiol benzoate caused a decrease in mitotic activity, a decrease in total cell population, and a further thinning of the epidermis. The lower concentration of topically applied estrogen produced more stimulation than the higher concentration; this was interpreted as inhibition due to the absorption and subsequent high systemic estrogen concentration. In 1946, one of us reported [10] that similar proliferative changes could be induced in senile (atrophic) human skin by the topical application of estrogen. In subsequent studies,[11] the effect of estrogen and testosterone applied to normal and senile skin was investigated. There was some suggestion in these studies of improvement of the elastic fibril network, and in recent reports Chieffi [12] described an increase of skin elasticity following topical application of estrogen but observed no increase after use of testosterone.

Other steroids have also been observed to affect the skin: Castor and Baker have shown that local application of cortisone or adrenal cortex extract [13] directly to the skin of the rat (or injection of corticotropin [ACTH] [14]) results in thinning of the epidermis, decrease in the size of the cells, atrophy of the hair follicles and sebaceous glands, and decrease in the collagenous tissue of the dermis. The elastic fibril network seems not to be affected.

As a continuation of our previous studies, the effects of local application of a variety of pure crystalline steroids were investigated, with the use of compounds, dosage levels, and techniques of investigation not hitherto employed.

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8. Dunaif, C. B., and Finerty, J. C.: The Effects of Estrogen Administration upon Epidermal Proliferation, J. Invest. Dermat. **15**:363-371, 1950.

9. Bullough, H. F.: Epidermal Thickness Following Estrone Injections in the Mouse, Nature, London **159**:101-102, 1947.

10. Goldzieher, M. A.: The Effects of Estrogens on Senile Skin, J. Gerontol. **1**:196-201, 1946.

11. Goldzieher, J. W.: The Direct Effect of Steroids on the Senile Human Skin, J. Gerontol. **4**:104-112, 1949.

12. Chieffi, M.: An Investigation of the Effects of Parenteral and Topical Administration of Steroids on the Elastic Properties of Senile Skin, J. Gerontol. **5**:17-22, 1950; The Effect of Topical Estrogen Application on the Elastic Properties of the Skin of Elderly Males, read before the third annual meeting of the Gerontological Society, Inc., St. Louis, Nov. 12-13, 1950.

13. Castor, C. W., and Baker, B. L.: The Local Action of Adrenocortical Steroids on Epidermis and Connective Tissue of the Skin, Endocrinology **47**:234-241, 1950.

14. Baker, B. L.; Ingle, D. J.; Li, C. H., and Evans, H. M.: Growth Inhibition in the Skin Induced by Parenteral Administration of Adrenocorticotropin, Anat. Rec. **102**:313-332, 1948.

MATERIALS AND METHODS

Forty-one serial studies were carried out on 27 elderly volunteers (11 women and 16 men) ranging in age from 62 to 84 years. The mean age was 77 years. These patients were selected after thorough physical examination and laboratory studies. Two patients showed residual signs of old hemiplegias, one had bilateral varicose ulcers, and one patient was in mild congestive failure. Chemical determinations included estimations of blood sugar, uric acid, urea nitrogen, and chloride and serum calcium, phosphate, protein, sodium, chloride, and cholesterol. Four patients showed a moderately increased serum cholesterol, one a low fasting blood sugar, and one an increased blood urea nitrogen level. All other results were within normal limits. Urinary hormone assays were carried out on pooled, refrigerated 48- to 72-hour specimens. Urinary 17-ketosteroids were extracted with ether after acid hydrolysis, subjected to Girard "T" fractionation, and measured colorimetrically by the absolute alcohol technique of Callow and associates.[15] Estrogens were extracted by the method of Engel and co-workers [16] and determined fluorometrically on the Farrand fluorometer, using the filter system and fluorescence

TABLE 1.—*Effect of Steroids on Skin*

Steroid	No. in Series	Dose, Mg./Day	Oil Carrier	Duration of Treatment, Days	Histological Changes
Estrone	1♀	2	+	45	+
	1♀	5	+	15	0
	1♀, 1♂	5	+	45	+, ±
	1♀, 2♂	9-10	2:0	45, 100	0
			1:+	9 mo.	+→−
Alpha-estradiol	1♂	5	0	45	+
	2♀, 2♂	5	+	45	+, +, 0, 0
Beta-estradiol	1♀	5	0	45	+
	3♀, 1♂	5	+	45	+, +, +, ±
Testosterone	1♂	2	0	45	0
	1♀, 1♂	5	0	45	0, ±
	2♀, 2♂	5	+	45	+, +, +, 0
	3♂	10	+	45	+, +, +
Methylandrostenediol	2♂	5	0	45	+, 0
	2♀, 1♂	5	+	45	+, ±, 0
Pregnenolone	1♀, 4♂	4	+	45	± (3), 0 (2)
Calciferol	1♀, 3♂	4	+, 0	45	±, 0 (3)

development recommended by Bates and Cohen.[17] Gonadotropins were isolated by ultrafiltration [18] and assayed (by serial dilutions) on 21- to 25-day-old cancer-free white (C. F. W.) mice, using 100% increase in uterine weight as a positive response. Determination of the response of these mice to International Standard pregnant mare's serum was done simultaneously, and thus the results of urinary extract assays were expressed as international units of follicle-stimulating hormone. Details of these studies are reported elsewhere.[19]

15. Callow, N. H.; Callow, R. K., and Emmens, C. W.: Colorimetric Determination of Substances Containing the Grouping—CH_2CO—in Urine Extracts as an Indication of Androgen Content, Biochem. J. **32**:1312-1331, 1938.

16. Engel, L. L.; Slaunwhite, W. R.; Carter, P., and Nathanson, I. T.: The Separation of Natural Estrogens by Countercurrent Distribution, J. Biol. Chem. **185**:255-263, 1950.

17. Bates, R. W., and Cohen, H.: Experimental Basis for Selecting the Optimal Conditions for Quantitative Fluorimetry of Natural Estrogens, Endocrinology **47**:166-181, 1950.

18. Gorbman, A.: Ultrafiltration of Urine for Collection and Biological Assay of Excreted Hypophyseal Hormones, Endocrinology **37**:177-190, 1945.

19. Goldzieher, J. W.; Rawls, W. B.; Roberts, I. S., and Goldzieher, M. A.: Studies on Aging: Correlation of Skin Morphology with Age and Hormone Excretion, J. Gerontol. **7**: 47-53, 1952.

The steroids investigated were estrone, alpha-estradiol, beta-estradiol, testosterone, pregnenolone, methylandrostenediol, and calciferol. The treatment schedules are indicated in Table 1. The crystalline steroid to be tested was dissolved in ether-alcohol solution (in some cases with a trace of light liquid petrolatum [light mineral oil] added to prevent mechanical loss of crystals from the skin surface). The solution was sprayed twice daily through a 27-gauge needle attached to a 2-cc. syringe directly onto a marked, 3- by 3-in. (7.6- by 7.6-cm.) area of skin located on the upper anterior or anteromedial surface of the thigh.

Biopsy specimens of the skin were obtained before the start of treatment and every 15 days thereafter for the duration of the experiment, which was usually 45 days. After induction of local anesthesia with 1% procaine hydrochloride solution, a disc of skin was excised with a 4- to 6-mm. Keyes punch and fixed immediately in a 1:4 dilution of Bouin's fluid (a mixture of formaldehyde solution, glacial acetic acid, trinitrophenol, and distilled water). The tissues were embedded in paraffin, sectioned, and stained by the hematoxylin and eosin, picrocarmine, Weigert-Van Gieson, Unna-Pappenheim, Feulgen, and Turchini methods. The sections were then coded, so that the examiner knew merely the correct sequence of the biopsy specimens in each series; only after morphological interpretation was completed and set down in writing was the material uncoded and grouped according to the steroid administered. Morphological criteria were the following: (1) width of the epidermis (number of cell layers), (2) presence and size of epithelial pegs projecting into the cutis and the corresponding presence or absence of papillae, (3) size and differentiation of epidermal cells, (4) amount and distribution of keratohyalin, (5) amount and distribution of nucleic acids, (6) vascularity and cellularity of the cutis, (7) degree of hyalinization of the collagenous fibrils, (8) amount of elastic fibrils and their state of preservation, fragmentation, or degeneration; existence of new fine elastic fibrils.

At the same time that biopsies were performed, the reflectance spectrum of the skin was also determined. Both the visible and the ultraviolet regions were studied by means of an apparatus based on a Beckman Model DU spectrophotometer. Details of theory, construction, and mode of operation of this device have been published elsewhere.[20] Suffice it to say that the reflectance spectrum of an opaque surface (e. g., the skin) is analogous to the absorption spectrum of solutions. Absorption bands of solutions may represent the presence and concentration of specific chemical constituents, and in reflectance spectra absorption bands have the same significance. For example, our studies suggest that absorption at 260 mμ is characteristic of nucleic acids; absorption at 290 mμ (and possibly also at 275 mμ) seems to be related to the presence and amount of keratohyalin material within the epidermis.

RESULTS

Age, Hormone Excretion, and Skin Morphology.—The known gradual decrease in excretion of urinary 17-ketosteroids with advancing age was noted in our material. Correlation of senile atrophy of the skin with age and with urinary excretion has been discussed in detail elsewhere.[19] In general, the senile atrophy of the skin grew more pronounced with advancing age and became especially prominent after the age of 70. No direct correlation of ketosteroid, estrogen, or gonadotropin excretion with skin morphology was found.

Morphological Alterations During Steroid Therapy.—The exact scheme of treatment and the results as evaluated in sections stained with hematoxylin and eosin (Morphological Criteria 1, 2, 3, 6) are shown in Table 1.

1. Estrone: Of seven patients treated topically with estrone, three showed a definite response, two an equivocal response, and two no response. In one instance

20. Goldzieher, J. W.; Roberts, I. S.; Rawls, W. B., and Goldzieher, M. A.: "Chemical" Analysis of the Intact Skin by Reflectance Spectrophotometry, A. M. A. Arch. Dermat. & Syph. **64**:533-548, 1951.

9 to 10 mg. of estrone was applied daily for a continuous period of nine months. Within several weeks, a patchy brownish pigmentation appeared and persisted for approximately a month. After this interval, ordinary daily cleansing caused the upper pigmented layers to peel off, in much the way a sunburn does, and no further pigmentation was seen. Of particular interest is the fact that this skin showed progressive epidermal atrophy, as well as a decrease in the picrocarmine-positive material, after five to six months of this intensive treatment (Fig. 1); there was a corresponding decrease in keratohyalin and nucleic acid (?) bands of the reflectance spectrum (Fig. 2). While epidermal atrophy has been reported in experimental animals as mentioned before, we do not believe that this has been observed previously in man.

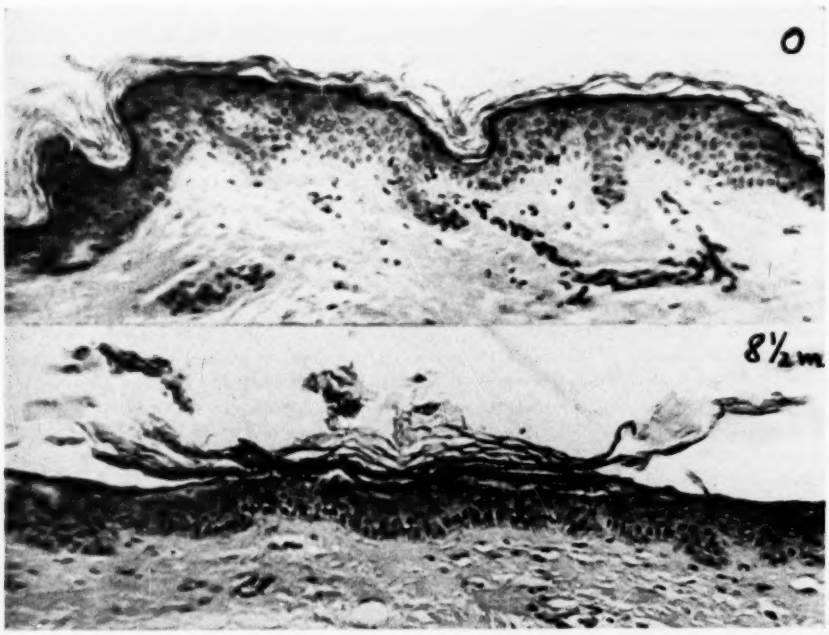

Fig. 1.—Appearance of epidermis before (upper part) and eight and a half months after (lower part) local application of 9 mg. of estrone daily to a male skin. Observe decrease in epidermal thickness and loss of the papillae, with consequent straightening of the line formed by the basal layer. Hematoxylin and eosin stain.

2. Alpha-Estradiol: Five patients were treated, four with oil as carrier in the spray, one without oil carrier. Proliferation, increase of papillae, and increase in keratohyalin were seen in three, and there appeared also to be new formation of fine elastic fibrils. One showed no change, and one showed slight regressive changes toward the end of the experimental period.

3. Beta-Estradiol: Of five patients treated with beta-estradiol, four showed increased thickness of the epidermis and/or progressive development of the rete pegs and papillae. The degree of proliferation was comparable with that found with

alpha-estradiol. Only two patients showed progressive increase in keratohyalin, and in two subjects some new formation of elastic fibrils appeared to be present.

4. Testosterone: At dosage levels of 2 and 5 mg. per day, without oil carrier in the solvent, no proliferative response was visible. At 5 or 10 mg. per day, using a trace of oil in the solvent, histological evidence of proliferation was observed in six of seven patients. In these same patients, an increase in keratohyalin granules was present (Figs. 3 and 4). In two patients there appeared to be some increase of the elastic fibril network.

5. 17-Methylandrostenediol: At the 5-mg.-per-day dose level, with or without oil carrier, minimal but definite signs of proliferation were seen in two of five sub-

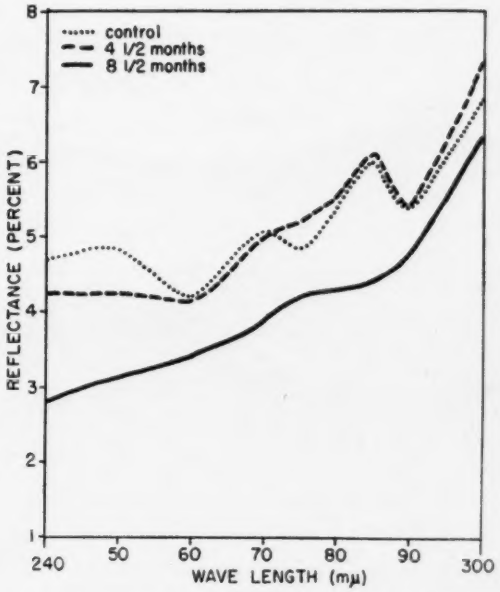

Fig. 2.—Ultraviolet reflectance spectrum of skin of patient Ho. shown in Figure 1. He received 9 mg. of estrone in an oil carrier daily. Observe presence of absorption bands at 260, 275, and 290 mμ in the control skin, decrease in the 260- and 275-mμ bands at four and a half months, and almost complete disappearance of all bands at eight and a half months.

jects. A questionable increase of the keratohyalin material was seen in two, and possibly some alteration in the elastic network was present in one patient.

6. Pregnenolone; Calciferol: Five patients were treated with pregnenolone and four with calciferol. Only equivocal or negative results were obtained. No appreciable changes in keratohyalin granules or the elastic fibril network were observed.

Alteration of Cellular Constituents During Steroid Application.—Increase in the keratohyalin granules was observed in most instances in which epidermal proliferation occurred and in all instances in which such proliferation was substantial. The absorption bands at 275 and 290 mμ correlated well with the histochemical alterations observed. Changes in the elastic fibril network are considerably more difficult to evaluate; however, alterations were observed during treatment with estrone and

alpha-estradiol, to some extent with beta-estradiol, and possibly with testosterone and 17-methylandrostenediol. No alterations whatever were noted during administration of pregnenolone or calciferol.

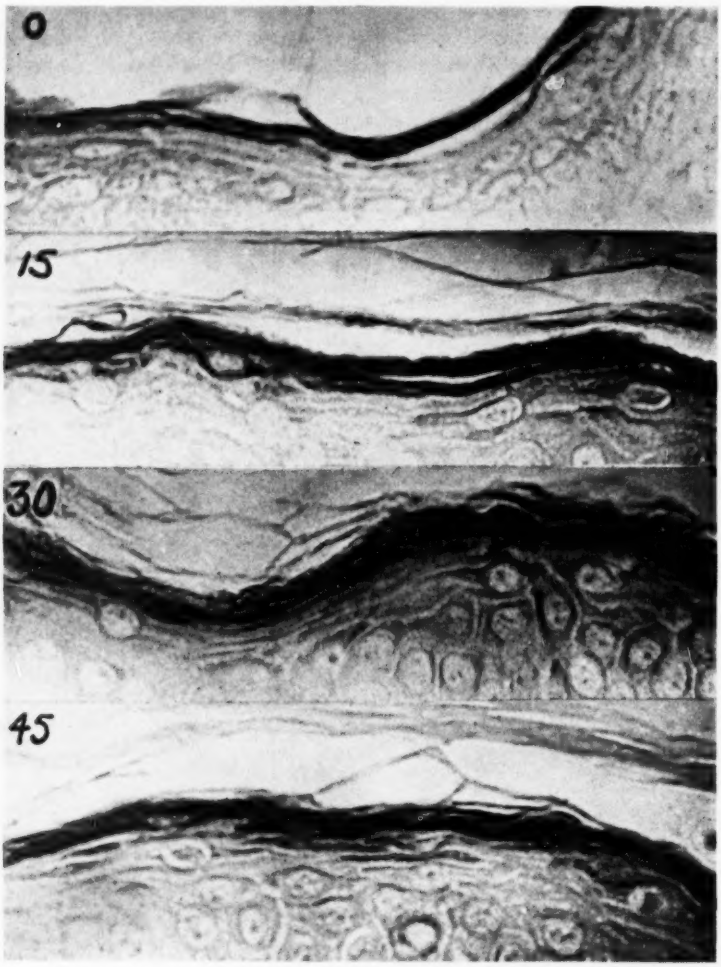

Fig. 3.—Picrocarmine stain, showing keratohyalin granules in the epidermis and their increase during local application of testosterone, 5 mg. per day. Note the increasing number of layers of squamous cells showing granulation.

Attempts were made by three different methods to study changes in nucleic acids of the epidermal cells. The Turchini stain, as described by Glick,[21] did not give satisfactory results in our hands. Currently available dyes for the Unna-

21. Glick, D.: Techniques of Histo- and Cyto-Chemistry, New York, Interscience Publishers, Inc., 1949.

Pappenheim stains yielded inconsistent results in Bouin-fixed tissues, despite a number of modifications. Staining with the Feulgen method also showed considerable variation in the intensity of staining from slide to slide, although each series of biopsy sections was stained simultaneously; in these circumstances quantitative evaluation of changes was not feasible. As the information regarding absorption at 260 mμ obtained by reflectance could not be compared satisfactorily with that obtained by other methods, it was felt that definite conclusions should not be based on the spectroscopic data unsupported by other evidence.

There is ample clinical and experimental evidence that injections of estrogen or testosterone cause an increase in skin circulation.[22] Recently, cyclic variations

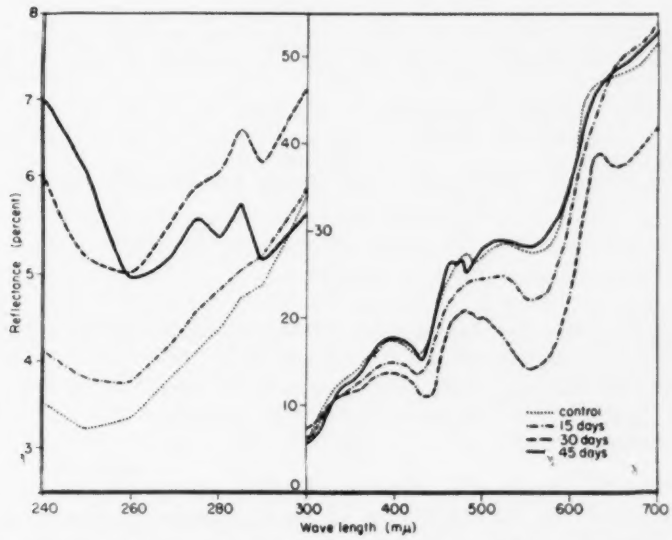

Fig. 4.—Reflectance spectrum of skin of patient Mo., a man aged 70, shown in Figure 3. He received 5 mg. of testosterone in an oil carrier daily. The 260-, 275-, and 290-mμ bands develop progressively; no consistent alterations are seen in the visible spectrum.

associated with the hormonal alterations of the menstrual cycle have been demonstrated by reflectance spectrophotometry. Our technique of spectrophotometry differed from that of Edwards and Duntley [23] in that an automatic recording device was not available. As a consequence, a certain amount of pressure was maintained at the periphery of the region studied for periods up to 15 to 20 minutes. This obviously influenced the local circulation and the ratio of oxyhemoglobin to reduced hemoglobin, and consequently no attempt was made to draw conclusions from the respective hemoglobin absorption bands in our spectral curves.

22. Edwards and Duntley.[4] Edwards, E. A.; Hamilton, J. B.; Duntley, S. Q., and Hubert, G.: Cutaneous Vascular and Pigmentary Changes in Castrate and Eunuchoid Men, Endocrinology **28**:119-128, 1941.

23. Edwards, E. A., and Duntley, S. Q.: The Pigments and Color of Living Human Skin, Am. J. Anat. **65**:1-33, 1939.

Individual Response to Different Steroids.—In 10 instances it was possible to evaluate the effect of two or even three steroids on the same patient (Table 2). Among patients who showed a definite response to testosterone, methylandrostenediol was entirely ineffective in one patient and active but less effective in a second. It is of interest also that this second patient, who responded to both testosterone and methylandrostenediol, showed no response to alpha-estradiol at the level of 5 mg. per day. In a third patient, in whom there was adequate response to testosterone, alpha-estradiol at the 5-mg. level produced, if anything, some atrophy of the epidermis. The response to pregnenolone in this subject was equivocal at best. In a fourth patient there were a definite though slighter response to beta-estradiol and a very doubtful response to calciferol.

In one patient (Ha.) two courses of testosterone, with and without oil carrier, failed to produce histological alterations, and equivocal changes resulted from the application of methylandrostenediol, both with and without oil carrier. Two patients

TABLE 2.—*Response of Same Patient to Different Steroids*

Patient	Testosterone	M. A. D.*	Estrone	Alpha-Estradiol	Beta-Estradiol	Calciferol	Pregnenolone
Od. ♂	++	0	..	..	..	..	..
Fl. ♂	++	+	..	0	..	..	..
Be. ♂	++	..	..	—†	..	..	±
Dr. ♀	++	..	..	..	+	♀	..
Ha. ♀	0/0	±/±	..	..	..	..	..
Mo. ♂	+	..	.	..	..	0	..
He. ♂	± (l. d.)‡	..	..	..	..	0	..
Da. ♀	....	..	0	..	±	..	..
Ma. ♀	....	..	0	..	±	..	..
Fu. ♂	....	..	..	..	±	0	..

* M. A. D. is methylandrostenediol.
† Regression.
‡ L. d. means low dosage level.

showing moderate response to testosterone exhibited no response to calciferol. Of particular interest are Patients Da. and Ma., in whom no response was seen following the application of estrone, but in whom a minimal and a definite response, respectively, occurred after beta-estradiol application. One patient showing a minimal response to beta-estradiol failed to respond to the administration of calciferol.

COMMENT

Method of Application.—The use of topical application in these experiments warrants some discussion. It is well known that in various tissues, for example, the cock's comb, the nipple of the breast, and the vaginal epithelium, topical application is by far the most effective method of producing a response. This technique has the advantage of a direct contact between the agent under study and the target organ; moreover, it eliminates the problem of metabolic alteration or inactivation which is encountered when steroid hormones enter the circulation on their way to the target organ. Furthermore, topical application provides a means of attaining almost any desired concentration at the chosen site and reduces the unwanted systemic side-effects to a minimum. It should be pointed out also that topical effectiveness of "sex" steroids is not limited to the secondary sexual organs, for

even the nasal mucosa in atrophic rhinitis has been shown to respond (to local applications of steroids) with epithelial proliferation.[24]

Extent of Epidermal Changes.—It was noted throughout this study that the degree of epidermal proliferation and thickening was not as pronounced as in our previous investigations. This may be due to one or both of the new variables introduced in this series of experiments. The use of a highly volatile solvent with only a minimum of oil carrier or no oil at all may be a relatively inefficient way to promote an interaction between the steroids and the skin; the beta-estradiol and testosterone experiments (with oil versus without oil) point strongly in this direction. It is known that alcoholic solutions of steroids are optimal for absorption through the skin into the systemic circulation; with agents of lower solvent power, such as liquid petrolatum (mineral oil), petrolatum (petroleum jelly), or wool fat (lanolin), the absorption into the system is less, but the local effects are greater. It is possible that our solvent contained insufficient nonvolatile material to permit adequate, maintained contact with the steroid in solution (i. e., not merely as insoluble crystals deposited on the skin) and gradual, continued diffusion into the lower, active layers of the epidermis.

The second factor may well be the high dosage level investigated in this series of experiments. In view of the studies on animals mentioned previously, and in view of the distinct atrophy of the epidermis observed in the patient maintained on very high estrogen levels for nine months (and the possible regression observed in another patient at 45 days), it is conceivable that in these experiments the optimal (stimulative) level has been exceeded. It may be that a range of dosage exists in which the proliferative response is neutralized more and more by the progressively increasing inhibitory effect. This hypothesis would account satisfactorily for the variable effects of estrogens at different dosage levels as observed in this study. This reaction pattern might also account for the fact that the biologically inactive beta-estradiol was occasionally more effective at the 5-mg. level than was an identical amount of alpha-estradiol.

In this connection, the experiments of Dunaif and Finerty require some comment. These investigators found inhibition of epidermal mitotic activity when estrogen was administered (either topically or by ingestion) in doses which produced systemic effects. They concluded, therefore, that inhibition of mitotic activity is a consequence of systemic absorption, in contrast to the purely local stimulative effect. The fact that their experimental animals showed systemic effects of estrogen absorption at these high levels of treatment is evident; to assume that this systemically absorbed estrogen is in any way causally related to the inhibition of epidermal mitosis is another matter. Several observations made during the course of our studies speak against this hypothesis. The male patient treated with 9 mg. of estrone daily for a prolonged period failed to show systemic effects (nipple tenderness, testicular atrophy, etc.) such as are observed when substantial amounts of estrogen are actually absorbed through the skin.[25] While vaginal smears were not studied during this phase of our investigation, no pronounced systemic estrogen effects (masto-

24. Mortimer, H.; Wright, R. P., and Collip, J. B.: Atrophic Rhinitis: The Constitutional Factor and the Treatment with Oestrogenic Hormones, Canad. M. A. J. **37**:445-456, 1937.

25. Goldzieher, M. A., and Goldzieher, J. W.: Toxic Effects of Percutaneously Absorbed Estrogens, J. A. M. A. **140**:1156, 1949.

dynia, vaginal bleeding, etc.) were noted in any of the female patients treated with estrogen. In general, it is not unusual to find a given organ or tissue reacting in diametrically opposite fashion to different dosage levels of the same substance (e. g., the reaction of the endometrium to diethylstilbestrol). Hence the burden of proof in this instance rests upon those who believe that epidermal atrophy is produced by a different mechanism from that operative as a stimulus at lower dosage levels. The mechanisms of both cellular stimulation and cellular inhibition require further study.

Dermal Effect.—Steroids have been observed to produce changes also in the dermis. On the one hand, alteration of the elastic network has been observed in a number of cases. Suggestive changes in the collagenous fibrils have also been seen, but as yet there exists no satisfactory yardstick for serial comparative observations of these changes. Recently, Chieffi has reported definite increase in elasticity following the topical application of estrogen. This is not to be equated with elastic fibril changes, for elasticity as measured by Chieffi is the sum total of alterations in the elastic fibrils, collagenous fibrils, capillary filling, turgor of the tissues, and perhaps even the hydrostatic pressure of the interstitial fluid. It may be pointed out that steroids are known to have a profound effect on the intracellular and extracellular electrolytes and water balance. It is, therefore, likely that the topical application of steroids produces changes of the cells with a consequent change in the turgor and resiliency of the tissues. Quantitative studies of this phenomenon have not as yet been undertaken, to our knowledge.

Dermotropic Versus Sexual Effects.—It is most important to note that the dermotropic effect of these various steroids does not run parallel with, and may well be entirely dissociated from, their sexual effects. This is not surprising, for it is well known that sexual effects do not necessarily run parallel with metabolic activity as regards electrolytes, nitrogen retention, etc. Methylandrostenediol, for example, has definite nitrogen-retaining effects with low androgenic activity. Cortisone has no "sexual" effect and causes definite atrophy of the epidermis and dermis. In our studies, an estrogenically inert estrogen (beta-estradiol) and an androgen of a very low androgenic potency were found to be effective in causing proliferation of atrophic human skin. It seems not unlikely, therefore, that a dosage level of a steroid or a combination of steroids can be found which will yield optimal proliferative response with minimal systemic effects.

Relation of Steroid Effects to the Process of Senescence.—Proliferation of the epidermal cells after administration of sex hormones in the castrated animal proves that the atrophy of the epidermis following castration is due to the lack of these hormones, which are apparently necessary for the maintenance of the normal skin. It would seem that the atrophy of the skin noted in old age represents a related phenomenon. The senile changes probably are of a more complex nature than those seen in the castrate, for the degree of atrophy in the senile individual increases with advancing years, even though there is no further measurable decline in gonadal hormone production. The evidence presented in this and in earlier papers, i. e., the proliferation of the epithelium and the increased vascularity and elasticity of the dermis following administration of steroid hormones, corroborates the view that inadequate secretion of these hormones plays an important role in the pathogenesis of senility, at least so far as the skin is concerned.

This view is in accord with the known metabolic effects of the steroid hormones, which are predominantly of the anabolic type; in senility the loss of body substance and the decrease in cell population and cell size are expressions of the prevalence of catabolism over anabolism. It remains to be shown whether these steroid hormones produce their anabolic effects directly by their impact on the cells or indirectly, for instance, by activation of enzyme systems.

SUMMARY

Forty-one serial studies of the effects of topically applied steroids were carried out on the skin of 27 elderly patients. The results were evaluated by serial skin biopsy specimens studied morphologically and histochemically, as well as by analysis of the reflectance spectra of the intact skin.

Administration of estrone, alpha-estradiol, and testosterone elicited proliferation of the epidermis, progressive development of the rete pegs and papillae, and an increase in the production of keratohyalin granules. New formation of elastic fibrils and increased vascularization of the cutis were also noted, especially after application of estrogens. Spectrophotometry showed changes in absorption bands at 275 and 290 mμ which correlated well with the histological changes in keratohyalin formation.

The estrogenically inactive beta-estradiol and the androgenically weak 17-methylandrostenediol showed comparable effects. Thus, dermotropic effects of the steroids did not parallel their "sexual" activity. Pregnenolone and calciferol caused no changes.

Administration of steroids at a high dosage level did not cause increased proliferation; actually, the effectiveness was less, and in several instances atrophy of the skin was produced by prolonged administration of estrogen. The inhibitory effect of high doses does not seem to be due to a systemic reaction following the percutaneous absorption of the steroids.

Miss Phyllis R. Epstein gave technical assistance.

* Dr. Edward Henderson, of Schering Corporation, Bloomfield, N. J., supplied ample quantities of pregnenolone, testosterone, and alpha-estradiol. Dr. Kenneth W. Thompson, of Organon, Incorporated, Orange, N. J., supplied estrone, beta-estradiol, and methylandrostenediol. Dr. J. Waddell and Dr. G. H. Kennedy, of E. I. du Pont de Nemours & Company (Inc.), Wilmington, Del., supplied crystalline vitamin D_3.

REVIEW OF THE PSYCHOTHERAPY OF WARTS

H. V. ALLINGTON, M.D.
OAKLAND, CALIF.

AS A BASIS for judging the value of any therapy for warts, one must first consider what is known about warts and their behavior.

It is generally agreed that warts are caused by a virus. Their infectious nature is suggested by their occasional occurrence in epidemic form.[1] The appearance of warts in linear arrangement along a scratch mark and on opposing surfaces of digits (kissing warts) suggests their inoculability.

A number of workers, beginning with Jadassohn [2] and including Wile and Kingery [3] in this country, have shown that warts can be transmitted by intracutaneous inoculation of wart material and that the infectious agent is filtrable. Hilleman [4] states that the wart virus is small in that it will pass Berkefeld filters of all porosities. The final proof of the virus origin of warts seems now at hand in the work of Strauss, Bunting, and Melnick.[5] They demonstrate with the electron microscope the presence of spherical virus-like particles in crystalline arrangement in suspensions of material obtained from human warts. The same warts show histologically intranuclear inclusion bodies and solid or vacuolated cytoplasmic masses in the rete cells suggesting the presence of virus material. Blank, Buerk, and Weidman [6] and Lyell and Miles [7] have also reviewed the question of inclusion bodies indicating virus activity in warts. Some differences in their findings and conclusions remain to be resolved.

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1. McLaughlin, A. I. G., and Edington, J. W.: Infective Warts in Workers Using Bone Glue, Lancet **2**:685 (Sept. 18) 1937.

2. Jadassohn, J.: Sind die Verrucae vulgares Übertragbar? Verhandl. deutsch. dermat. Gesellsch. **5**:497, 1896.

3. Wile, U. J., and Kingery, L. B.: The Etiology of Common Warts, J. A. M. A. **73**:970 (Sept. 27) 1919.

4. Hilleman, M. R.: Viruses of Special Interest to the Dermatologist: A Review, Arch. Dermat. & Syph. **61**:210 (Feb.) 1950.

5. (*a*) Strauss, M. J.; Bunting, H., and Melnick, J. L.: Virus-like Particles and Inclusion Bodies in Skin Papillomas, J. Invest. Dermat. **15**:433 (Dec.) 1950; (*b*) Eosinophilic Inclusion Bodies and Cytoplasmic Masses in Verrucae, ibid. **17**:209 (Oct.) 1951.

6. Blank, H.; Buerk, M. S., and Weidman, F.: The Nature of the Inclusion Body of Verruca Vulgaris: A Histochemical Study of Nucleotids, J. Invest. Dermat. **16**:19 (Jan.) 1951.

7. Lyell, A., and Miles, J. A. R.: Myrmecia: A Study of Inclusion Bodies in Warts, Brit. M. J. **1**:912 (April 28) 1951.

It is probable that the same virus is responsible for all the common varieties of infectious warts, verruca vulgaris, verruca plana juvenilis, verruca plantaris, and condyloma acuminatum. Some of the evidence supporting this is reviewed by Goodman and Greenwood [8] and by Blank, Buerk, and Weidman.[6]

Some animals, including cattle, horses, dogs, and rabbits, have warts, and experimental cross inoculation between animals and man has been reported.[9] However, the validity of these reports has recently been questioned.[6]

All will agree that warts are common, although the exact incidence is not known. Osborne and Putnam [10] state that between 5 and 6% of patients seen in their private practice between 1927 and 1930 were seen because of warts. Both they and Hellier [11] believe that the incidence of warts is higher in recent years. Hellier [11] states that in 1949 one patient in six of all new patients attending the Skin Department at Leeds Infirmary, Leeds, England, had warts.

Warts are commoner in children and young adults than in older persons. Rulison,[9b] whose statistical study of 921 cases constitutes the greatest contribution to knowledge of the natural history of warts, places the highest incidence of warts of all types in the age period from 16 to 20 years. His figures show that the incidence falls off rapidly after the age of 25. Strauss, Bunting, and Melnick [5b] found much the same age distribution in their analysis of 104 cases of common and plantar warts, as did Osborne and Putnam [10] in a study of 765 cases of warts.

It is common knowledge that warts may disappear spontaneously. Memmesheimer and Eisenlohr [12] followed 70 patients used as controls in an experiment on psychotherapy of warts and found that in 20, or 28.6%, the warts had cleared spontaneously at the end of a six months' observation period. Rulison,[9b] from an analysis of 40 case records, placed the average duration of an initial attack of common warts without treatment at approximately two years three months. In 22 of the 40 cases a second separate attack occurred later. The average duration of the second attack was approximately three years one month.

Montgomery and Montgomery [13] noted that in their series of patients with plantar warts treated with x-rays the average duration prior to observation was 11 months. Strauss and his co-workers [5b] found the duration of the warts in their series prior to treatment to be 5.5 months for plantar warts and 9.2 months for common warts. Bloch [14] found the average duration of the lesions to be between 1.5 and 2 years for common warts and a little less for verruca plana juvenilis in the patients he treated by suggestion.

8. Goodman, J., Jr., and Greenwood, A. M.: Verrucae: A Review, Arch. Dermat. & Syph. **30**:659 (Nov.) 1934.

9. (*a*) Goodman and Greenwood.[8] (*b*) Rulison, R. H.: Warts: A Statistical Study of 921 Cases, Arch. Dermat. & Syph. **46**:66 (July) 1942.

10. Osborne, E. D., and Putnam, E. D.: The Treatment of Warts, Radiology **16**:340 (March) 1931.

11. Hellier, F. F.: The Treatment of Warts with X-Rays: Is Their Action Physical or Psychological? Brit. J. Dermat. **63**:193 (May) 1951.

12. Memmesheimer, A. M., and Eisenlohr, E.: Untersuchungen über die Suggestivbehandlung der Warzen, Dermat. Ztschr. **62**:63 (Sept.) 1931.

13. Montgomery, A. H., and Montgomery, R. M.: Roentgen Ray Therapy of Plantar Warts, New York J. Med. **41**:371 (Feb. 15) 1941.

14. Bloch, B.: Über die Heilung der Warzen durch Suggestion, Klin. Wchnschr. **6**:2271 (Nov. 26) 1927; 2320 (Dec. 3) 1927.

The reasons for spontaneous healing of warts are not known. Rulison's [9b] figures suggest that there may be familial differences in susceptibility. Strauss, Bunting, and Melnick [5b] and Blank, Buerk, and Weidman [6] find the eosinophilic intranuclear inclusion bodies and characteristic cytoplasmic masses more commonly in young warts than in those of longer duration. Perhaps this indicates a tendency to spontaneous gradual weakening and dying out of the virus without the need of any specific response on the part of the host. The lower incidence of warts in older age groups may reflect a natural resistance of older tissues to invasion by the wart virus or may be the result of prior infection with the development of specific immunity. I have recently been asking adults who come for wart treatment whether they have had warts previously and find that the answer frequently is "No." However, Rulison [9b] has shown that second and even third attacks of warts may occur.

Zwick [15] notes that in successful transmission experiments the inoculation must be made superficially into the epidermal layers and that appreciable mixture with blood or tissue juices interferes with the development of the transplant. He believes this indicates that some factor is present in the blood and tissue juices which is harmful to the wart virus. Findlay [16] states that dogs can produce an antiviral wart serum. Specific antibodies have been demonstrated in the blood of rabbits inoculated with material from warts.[17] It is assumed that similar specific antibodies are also formed in human beings. Findlay [16] states that after inoculating himself with three crops of warts he became immune to further inoculation. The serum, after hyperimmunization, acquired antiviral properties.

Efforts directed toward making a vaccine have been hampered by the inability thus far to culture the wart virus. Perhaps the work of Strauss and his associates [5a] points the way toward obtaining a relatively pure and concentrated suspension of wart virus. However, the amount of virus obtainable by their method will probably be too small to be of practical use in the production of wart vaccine.

Biberstein [18] has for a number of years used a crude wart autolysate as a vaccine. He gives his patients intradermal injections of it twice weekly. Approximately 68% of patients with verruca vulgaris, 88% of those with verruca plana juvenilis, and about the same percentage of persons with condylomata acuminata were cured either completely or except for a single or a few remaining warts, according to his figures. His patients received an average of 15 to 20 injections. Biberstein [18] believes that these apparent cures are the result of specific immunization to the wart virus.

15. Zwick, K. G.: Hygiogenesis of Warts Disappearing Without Topical Medication, Arch. Dermat. & Syph. **25**:508 (March) 1932.

16. Findlay, G. M.: Warts, in Andrewes, C. H., and others: A System of Bacteriology in Relation to Medicine, London, His Majesty's Stationery Office, 1930, Vol. 7, p. 257.

17. Kidd, J. G.; Beard, J. W., and Rous, P.: Certain Factors Determining the Course of Virus-Induced Tumors, Proc. Soc. Exper. Biol. & Med. **33**:193 (Oct.) 1935. Kidd, J. G.: A Complement-Fixation Reaction Involving the Rabbit Papilloma Virus (Shope), ibid. **35**:612 (Jan.) 1937.

18. Biberstein, H.: Immunization Therapy of Warts, Arch. Dermat. & Syph. **50**:12 (July) 1944.

Samek,[19] Biberstein,[18] Vollmer,[20] Conti,[21] and others have called attention to the inflammatory reaction which may occur in warts prior to spontaneous involution or before disappearing in apparent response to treatment. I have noted this reaction in several cases in my own practice. This has been considered by some to be similar to the Jarisch-Herxheimer reaction or to a specific antibody-antigen reaction.

Perhaps because warts are small, well-demarcated tumors and because they provoke no appreciable general reaction and in most cases no notable local inflammation, there is relatively little stimulus to antibody production. Thus, immunity develops much more slowly and is much less certain than in many of the more acute virus diseases.

Rulison [9b] believes that specific wart antibody formation probably occurs in human beings and that it may tend to limit the number of warts which form and to protect against reinfection, but he doubts that it is responsible for the disappearance of existing warts. He suggests that the development of large numbers of warts in a person indicates a deficiency or delay in production of antibodies.

Whatever the factors involved, it appears that at times the balance between susceptibility and immunity in warts must be a delicate one. Only a slight shift may be needed to cause their disappearance. In other instances, however, warts are most stubborn and resistant to treatment. Goodman and Greenwood,[8] Vollmer,[20] Lane,[22] and Belisario [23] review large numbers of treatment methods, each of which is used with apparent success at times but none of which is consistently successful. Because of their beneficial effect in rickettsial disorders and a few of the virus diseases, the new antibiotics were tried by many. There have been reports of isolated cases of success,[24] but the results when antibiotic therapy is tried in series of cases are again disappointing.[25] Even complete surgical removal may be followed by recurrence, presumably because some of the virus remains behind in the tissues. Because of this, Templeton [26] has compared warts to weeds in respect to their tendency, at times, to recur repeatedly in spite of apparently complete removal.

It is apparent that there are many features in the life history of warts about which there is uncertainty. The viability and distribution of the wart virus in nature and other important epidemiological data are lacking. There are only limited and imperfect figures on the incidence of warts. The articles by Rulison [9b] and Memmesheimer and Eisenlohr [12] give the only factual data on the average duration of

19. Samek, J.: Zum Wesen der suggestiven Warzenheilung, Dermat. Wchnschr. **93**:1853 (Nov. 28) 1931.

20. Vollmer, H.: Treatment of Warts by Suggestion, Psychosomat. Med. **8**:138-142 (March-April) 1946.

21. Conti, A. L.: Sindrome de pre-extincion de las verrugas planas juveniles, Rev. méd. la Plata **1**:50-51, 1949.

22. Lane, C. W.: Verrucae: A Dermatologic Problem, J. A. M. A. **144**:1361 (Dec. 16) 1950.

23. Belisario, J. C.: Warts and Their Treatment, Australian J. Dermat. **1**:20 (March) 1951.

24. Rose, S. J.: Aureomycin Ointment in Verruca Planae, A. M. A. Arch. Dermat. & Syph. **63**:135 (Jan.) 1951.

25. Hollander, L., and Hardy, S. M.: Failure of Aureomycin Hydrochloride Therapy in Warts, Arch. Dermat. & Syph. **62**:714 (Nov.) 1950. Beinhauer, L. G., and Gibson, W. S.: Aureomycin in the Treatment of Verruca Vulgaris, Urol. & Cutan. Rev. **53**:547 (Sept.) 1949.

26. Templeton, H. J.: Warts, California Med. **68**:23 (Jan.) 1948.

untreated warts and the percentage of these tumors which disappear spontaneously within a given time. Very little is known regarding the reasons for this spontaneous healing.

All this adds up to the fact that dermatologists have a very weak and uncertain base on which to judge the efficacy of any method of wart therapy.

Many writers have discussed the means by which psychotherapy may work.

Bonjour [27] believed that suggestion acts by lowering the blood pressure and thereby diminishing the amount of blood reaching the skin, resulting in atrophy of the wart.

Grumach,[28] Bloch,[14] Sulzberger and Wolf,[29] Vollmer,[20] Niedelman,[30] and others call attention to the circulatory changes which may occur under the influence of the autonomic nervous system. Blushing, pallor, and sweating, of course, commonly reflect emotional changes. Variation in temperature of the skin and changes in capillary permeability may result from psychic stimulus. Blistering, bleeding, and gangrene are also reported as occurring under psychic and hypnotic influence. This neurovascular mechanism is thought to produce local trophic and physicochemical changes which make the soil unsuitable for further activity of the virus.

Kalz [31] calls attention to the fact that histamine and acetylcholine are released under emotional stimulation and may be important in the pathogenesis of skin diseases. Hall [32] suggests that thromboplastin, present in the surrounding tissues but lacking in warts, may be inimical to the life of a wart and may play a part in the changes produced by psychotherapy. Sequeira, Ingram, and Brain [33] suggest that emotional stimuli may effect natural immunity through the endocrine glands.

Samek [19] found an inflammatory reaction, histologically as well as clinically, in warts healing after suggestion therapy. Hyperemia, edema, and infiltration of leucocytes and round cells occurred in the corium and papillary bodies. The epidermis showed an exaggeration of the degenerative changes noted regularly in warts in the prickle-cell and keratohyalin layers. Mitoses became less frequent in the lower layers of the stratum spinosum. Finally, the prickle-cell layer became thinned, a normal keratohyalin layer re-formed, and the degenerated cells flaked off. The inflammatory reaction persisted for two weeks after the warts had gone. Samek [19] considered these changes to be due to a psychic-reflex stimulation of the vessels of the papillary bodies, leading to an increased reaction capacity of the cutis.

Vollmer [20] compares these changes with those reported by Unna in warts healing spontaneously. He believes that cure by suggestion and spontaneous healing are

27. Bonjour, J.: Influence of the Mind on the Skin, Brit. J. Dermat. **41**:324 (Aug.-Sept.) 1929.

28. Grumach, L.: Über Suggestivbehandlung von Warzen, München med. Wchnschr. **74**:1093 (July) 1927.

29. Sulzberger, M. B., and Wolf, J.: The Treatment of Warts by Suggestion, M. Rec. **140**:553 (Nov. 21) 1934.

30. Niedelman, M. L.: The Management of Warts, Am. Pract. **2**:327 (Jan.) 1948.

31. Kalz, F.: Psychological Factors in Skin Disease, Canad. M. A. J. **53**:247 (Sept.) 1945.

32. Hall, F., in discussion on Obermayer, M. E.: Verruca Plana of the Face Treated by Posthypnotic Suggestion, Arch. Dermat. & Syph. **60**:1222 (Dec.) 1949.

33. Sequeira, J. H.; Ingram, J. T., and Brain, R. T.: Diseases of the Skin, Ed. 5, London, J. & A. Churchill, Ltd., 1947, p. 633.

the same process and that psychotherapy merely accelerates it. Goldsmith,[34] who discusses this subject, believes that warts are susceptible to psychogenic influence because they are unstable structures which already have a tendency to spontaneous regression.

The psychotherapy of warts began, no doubt, in prehistoric times with the practice of magic. According to Zwick,[15] magic is employed in every quarter of the globe by civilized as well as by primitive man, so generally as to make the practice almost universal. He details a number of methods which have been handed down from past generations, such as pressing or rubbing the wart with a piece of apple, pork, or a pea, and then disposing of the material used by throwing it away or burying it. The stage of the moon is often considered important. The warts are expected to disappear when the material used has rotted. Tying a thread tightly about the base of the wart and then burying the thread is another method used.

Zwick[15] reports that in North Africa warts are exposed to lightning or to the light of the new moon while an incantation is repeated. The aid of a special saint is sometimes invoked, or the blood of a hedgehog is applied to the wart. American folk medicine is illustrated in Mark Twain's classical novel, "The Adventures of Tom Sawyer.[35] The hero and his friend, Huck Finn, discuss the relative value of applying "spunk-water" in the middle of a woods at midnight as compared with that of burying a bean, half of which is covered with blood from the wart, at a crossroads at midnight in the dark of the moon. Disposing of a dead cat at midnight in a graveyard where someone who was wicked has been buried is also excellent for curing warts. The proper words to be spoken with each method are given.

A short summary of my paper on the use of liquid nitrogen in the treatment of warts,[36] which was presented at the meeting of the American Academy of Dermatology and Syphilology in 1948, was carried in a number of newspapers throughout the United States. After this, I received numerous letters and cards from self-styled wart healers. Many of them advised the application of some common household substance, such as iodine or castor oil or a bleaching solution. Saliva and urine were advised by several. The juices of a great variety of plants and weeds have been credited with curative effects.

Although it is well known that warts have disappeared on many occasions after this type of therapy, there are no statistics on which to evaluate it. Tom Sawyer quotes no figures as to his percentage of cures, and neither do the "medicine men," grandmothers, blacksmiths, or barbers who have practiced this art.

Bonjour[27] was one of the earliest and most enthusiastic of the physicians who have studied and practiced the psychotherapy of warts. He states that he began treating warts by suggestion in 1888. He had his patients place their hands on a piece of paper, and he then would draw the outline of the hand and mark in the warts in their natural size.[37] He then blindfolded his patients and touched the warts lightly with his finger or a small ring or charm while saying, "From today on you won't feel the warts any more and they will disappear; don't touch them

34. Goldsmith, W. N.: Recent Advances in Dermatology, Philadelphia, P. Blakiston's Son & Co., 1936, p. 126.

35. Twain, M.: The Adventures of Tom Sawyer, New York, Grosset & Dunlap, p. 56.

36. Allington, H. V.: Liquid Nitrogen in the Treatment of Skin Diseases, California Med. **72**:153 (March) 1950.

37. Bonjour, L.: À propos de verrues, Schweiz. med. Wchnschr. **54**:748 (Aug. 14) 1924.

again." In some cases he repeated the same procedure at monthly intervals up to six times. Often purely verbal suggestion, even when given casually at a social gathering, was sufficient, and treatment by letter was successful. The warts disappeared without trace in 10 days to four or five weeks. Although he presents no actual statistics, he states that by suggestion "we may expect a favorable result in all cases." According to Bloch,[14] Bonjour did not have a single failure in 30 years.

Bonjour [27] believed that the skin is an organ of expression and that it often reflects certain psychic processes by somatic symptoms, "especially if the skin has a pathological disposition to act thus." He believed that many skin diseases, such as eczema, erythroderma, hyperhidrosis, and urticaria, and also hay fever and asthma, were due to the action of the mind. He did not accept the infectious origin of warts but believed they were the result of a special congestion of the papillae and that they could be made to appear by suggestion. He also believed that simple suggestion suffices to cure warts and eczema, while a slight state of hypnosis is needed to cure cases of erythroderma, hyperhidrosis, urticaria, hay fever, asthma, and other similar conditions.

Isolated cases of disappearance of warts following suggestion were subsequently reported. Nini [38] notes one case in which the warts cleared after being touched with tap water with the claim that it was a new cure for warts; in another case the warts disappeared after being rubbed with earth from a shrine. Pech [39] reported the case of a young patient with numerous warts, a few of which were removed. The rest disappeared two weeks later after a severe emotional shock. Many writers have since reported, and most dematologists have noted, that at times all the remaining warts will disappear after the removal of one (*verrue mère*) or a few of them.

Grumach [28] used injections of 0.5 to 1 cc. of isotonic sodium chloride solution into the arm repeated at intervals of 8 to 14 days as a means of masked suggestion. The patients were told they were receiving a new and effective remedy for warts and that they would feel a slight burning or pain in the part of the body where the warts were located as a sign that the treatment was working. Of 18 patients so treated, 16 were cured within four months. The first signs of regression were noted as a rule in two to three weeks.

Bloch [14] reports the largest series of cases. He blindfolded his patients while they were in his consultation room. He explained to the more intelligent ones that they were being treated by suggestion. He then took them into a treatment room and seated them and placed their hands on the table of an electrical machine (*Pantostaten*). The apparatus was started, but none of the current was allowed to reach the body. It was utilized only for its sound effect. A drawing was made of the parts of the body involved and the localization of the warts marked. Then all warts were tinted with a coloring liquid, either eosin, methylene blue or red, or green ink. The patients were then taken back into the consultation room. The blindfold was removed, and they were directed never to touch the warts as long as a trace of the color persisted. They were then assured that the warts would be cured.

38. Nini, T.: Traitement des verrues par la suggestion? Presse méd. **31**:357 (March 3) 1923.

39. Pech, M.: Traitement des verrues par la suggestion? Presse méd. **31**:358 (March 3) 1923.

They were dismissed and asked to return in a few weeks. Occasionally, especially at the time of repeated suggestion after previous treatments were ineffectual, each wart was heavily "faradized." In isolated cases additional emphasis was given to verbal suggestion, but hypnosis was never used. He treated 178 patients having verruca vulgaris and 50 with verruca plana juvenilis. He was able to follow 179 of these patients and reported cure of 88.4% of those with verruca plana juvenilis and 44.1% of those having verruca vulgaris lesions. In the majority the warts cleared within a month. Although no control series was followed, Bloch felt that this high rate of cures within such a short period could not be laid to spontaneous healing.

Memmesheimer and Eisenlohr [12] used verbal suggestion and painting with methylene blue. In a few cases they also used electricity (faradization). They treated 70 patients and followed another 70 who were untreated. Their results showed 17 cures (24.3%) among the treated patients at the end of six months as opposed to 20 cures (28.6%) among the untreated. However, at the end of one month 11 of the treated patients were cured as opposed to only 2 of the untreated, and at the end of three months there were 14 cures in the treated group and only 5 in the untreated.

Goodman and Greenwood [8] treated eight patients who had plantar warts by the weekly intramuscular injection of isotonic sodium chloride solution. Cure occurred in six of the eight patients within three to six weeks.

I treated 84 patients who had warts with intragluteal injections of distilled water [40] as a control series in evaluating sulfarsphenamine in the treatment of warts. Of these, 47.6% were cured (37.7% of those with common warts, 72.2% of those with plantar warts, and 85.7% of those with juvenile plane warts). The majority received only one injection. Four received two injections, the second a month after the first, and one received three injections, again after another month. As nearly as could be judged, in the successfully treated patients involution had begun within the first two weeks in 55% and within the first month in 80%. These results did not differ significantly from those obtained with use of sulfarsphenamine.

Vollmer [20] treated more than 100 children with warts, most of whom had verruca plana juvenilis. He used a modification of Bonjour's and Bloch's methods of careful examination and diagramming of the warts. The patients were given the diagrams with the warts indicated in red or blue pencil and told to check the progress of the warts daily against the diagrams. The warts were painted with a colored fluid, and the patient was told not to wash the hands that day and not to touch the warts until they had gone. They were told to note carefully, and a faint tingling would be felt in the warts as a sign that they would soon disappear. If this was not felt, further treatment was indicated. Irradiation with red or blue light was done in some, or the parts were exposed to a noisy x-ray machine, although no actual radiation was used. A few children were told that the injections of routine immunizing agents, such as diphtheria toxoid, were wart remedies. Although definite figures are not presented, failure to cure verruca plana juvenilis was said to be a rare exception. Common warts responded more slowly, and failures amounted to about one-third of the number treated. The interval between treatment and cure varied from four days to seven weeks.

40. Allington, H. V.: Sulpharsphenamine in the Treatment of Warts, Arch. Dermat. & Syph. **29**:687 (May) 1934.

Belisario [23] reports success in a small percentage of cases with a routine similar to that of Bloch.[14]

Obermayer [41] reports one case in which the consultation of a psychiatrist was obtained and in which hypnosis followed by suggestion was apparently successful in curing long-standing juvenile plane warts. McDowell [42] reports a similar case in which numerous juvenile plane warts disappeared from the hands and face of a young woman after suggestion while the patient was hypnotized. Thiernesse [43] has treated warts by putting the patient to sleep and then suggesting that his warts will soon disappear. Several cases are reported with no failures or recurrences.

A number of writers, including Bloch,[14] Sulzberger and Wolf,[29] Vollmer,[20] and Hellier,[31] have suggested that except for methods involving total destruction, none of the wart treatments is in any way specific. They state that the results of different chemical and physical methods are no better than those obtained by suggestive procedures. It is considered that every therapeutic procedure implies a suggestive component and that it is reasonable to assume that, with the exception of destructive doses of radiation and surgery, all methods act mainly by suggestion. Observation of the patient by a physician may alone have a psychotherapeutic effect.[29] I have more than once seen patients in whom warts have disappeared during the interval between the initial examination and the date set for removal of the warts a week or two later.

In contrast to this point of view, it may well be that some of the methods of magic and of psychotherapy used in warts should not be considered as such. Zwick [15] divides them into two groups according to whether or not trauma is involved. He believes that trauma, such as rubbing, pressing, or tying a string about a wart, or injecting a substance into it, may establish a contact with tissue constituents which are deleterious to the wart and thereby cause curative disintegration. Biberstein [18] questions methods which include, for example, the injection of presumably unspecific or indifferent materials. He believes some of them may have a chemotherapeutic effect on the virus, may act as foreign proteins, may provoke the production of "reacting bodies," or may have an effect on the vegetative nervous system. On these grounds, he objects even to Grumach's [28] method of the intramuscular injection of isotonic sodium chloride solution.

The intramuscular injection of distilled water provokes sharp local pain. Because of its hypotonicity, it probably produces some degree of local tissue injury and indirectly exerts some minor protein shock effect. I believe that the use of electricity, such as the "faradization" that Bloch [14] and Memmesheimer and Eisenlohr [12] used in some of their cases, may have a direct physiological effect which confuses the issue with regard to psychotherapy.

The proponents of psychotherapy note that the success of any treatment for warts varies greatly from person to person. A method which is successful when applied by one person has often been a failure in the hands of another. They believe that this indicates that the method is less important than the person who applies it.

41. Obermayer, M. E.: Verruca Plana of the Face Treated by Posthypnotic Suggestion (Case Report), Arch. Dermat. & Syph. **60**:1222 (Dec.) 1949.

42. McDowell, M.: Juvenile Warts Removed with the Use of Hypnotic Suggestion, Bull. Menninger Clin. **13**:124 (July) 1949.

43. Thiernesse: Le traitement des verrues par la suggestion, Arch. Belges dermat. et syph. **4**:128, 1948.

Bonjour,[27] Bloch,[14] Sulzberger and Wolf,[29] Vollmer,[20] and others stress that the attitude of the therapist is important and that faith in the method and in his ability to apply it successfully is essential. They stress that in psychotherapy environment is important and that freedom from hurry, noise, and distraction is a requisite to success.

In general, it has been found that juvenile plane warts appear to respond much more readily to psychotherapy than do common warts. Cure is more difficult in cases in which the warts are numerous than in those in which they are few. The response to psychotherapy is better when the lesions are recent than when they have been present for a long time. Within limits, the younger the patient, the easier the cure, although Vollmer [20] states that psychotherapy is not effective in children under the age of 3 years and is worthless in patients who are mentally deficient. Sulzberger and Wolf [29] also state that psychotherapy usually fails in intellectually sluggish persons and is not successful in imbeciles and idiots.

It is not always possible to correlate the apparent psychic effect on the patient with the subsequent success or failure of the psychotherapy.[29] On the other hand, the receptivity or suggestibility of the patient has been considered as important by Bloch,[14] Memmesheimer and Eisenlohr,[12] and others. They believe that the stronger the emotional response on the part of the patient, the better the chance of cure. Memmesheimer and Eisenlohr [12] call attention to the effect of such intangible emotional factors as the Christmas season. They noted that in a number of the children whom they followed warts which were present prior to Christmas were found to be gone directly after the New Year.

It is difficult to draw definite conclusions regarding the efficacy of the psychotherapy of warts. No matter how much circumstantial evidence suggests that in individual cases warts have cleared as the result of psychotherapy, it is impossible to rule out coincidence. One must respect such workers as Grumach [28] and Bloch [14] and the results of psychotherapy which they report. The results which I obtained with distilled water, if this method can be considered psychotherapy, are similar to those of Bloch.[14] Because of the fairly high cure rate within a relatively short time, these figures speak for the efficacy of psychotherapy, but again one must wonder how many of these represent spontaneous cures. Memmesheimer and Eisenlohr,[12] who controlled their experiment in psychotherapy as carefully as they were able, obtained results which clearly illustrate the need for such control. Their cure rate, among both treated and control patients, was also much lower.

Bonjour's [27] unfailing success, his unwillingness to deviate from his theory of the psychic origin of warts, and the wide variety of conditions which he cured with seeming ease by psychotherapy mark him as an extreme enthusiast for this method. One is prone to discount his conclusions somewhat because of this obvious enthusiasm and the lack of statistical data in his papers.

Vollmer's [20] review of the subject is an excellent one, but his results are given in approximations only, and some of the methods which he used could be questioned as pure psychotherapy. The others who have written on this subject have based their conclusions on the results of treatment in a limited number of cases or on impressions rather than on exact figures.

One is still forced to agree with Goodman and Greenwood,[8] who stated 17 years ago that the lack of controlled investigations and the spontaneous disappearance of warts make this question a confused one.

In order properly to evaluate any therapy for warts, further knowledge is needed regarding the epidemiology and natural history of untreated warts. Facts are needed regarding immunology in order to help explain wart behavior with particular reference to spontaneous cure. Results of treatment must be accurately recorded and properly controlled.

In experimental studies, methods of psychotherapy must be chosen carefully in order to avoid introducing questionable nonpsychic influences. Conversely, control series will be difficult to obtain without subjecting the patients to some psychic stimuli.

The close cooperation of persons fully trained in psychiatry should be sought. It would be desirable to know whether wart patients in general show any significant psychological deviations from the normal. A psychiatrist should be able to help in choosing methods and techniques of psychotherapy which may be more suitable and effective than those described to date and of setting up adequate controls. The question of possible harm to the patient from improper psychotherapeutic procedure, as raised by Obermayer,[41] should be carefully considered.

Until a specific remedy for warts is discovered and made available for general use, their treatment will continue, at times, to be a difficult and distressing problem. The evidence that psychotherapy is an effective method of treatment for warts is inconclusive. More study is needed before the suitability and limitations of this procedure can be established.

INFLAMMATORY NODOSE LESIONS OF THE LOWER LEG

HENRY E. MICHELSON, M.D.
MINNEAPOLIS

NODOSE lesions of the lower leg are usually classified according to their characteristics; thus, we speak of three principal varities: (1) erythema nodosum, (2) erythema induratum, and (3) nodular vasculitis. Erythema nodosum was for many years considered to be an acute cutaneous disease, closely allied to erythema multiforme, and because it responded to salicylates, it was thought that it might be a rheumatoid disease. Erythema induratum is a term reserved to describe those indurative lesions which occur almost exclusively on the lower leg in cases of tuberculosis and which are known to be tuberculous in origin. Nodular vasculitis is a term that has been applied to a number of nodular conditions, the causation of which cannot be ascertained, but the morphology of which reveals the group to be closely aligned anatomically to the other two types. It is a widely inclusive term, embracing both acute and chronic conditions, and it has been applied to cases of nodular phlebitis and periphlebitic indurations.

ERYTHEMA NODOSUM

Erythema nodosum, in its manifestation as an idiopathic, acute disease, is well known to dermatologists, and, if all cases of the disease could be dismissed as idiopathic, no further discussion would be necessary. However, nodose lesions that could not be distinguished morphologically from the idiopathic ones have been observed after ingestion of certain drugs and also accompanying some systemic diseases; therefore, a nonidiopathic form was recognized, and the true nature of the condition gradually came under question. Doubt concerning its causation arose particularly when it was declared to be a manifestation of the reaction of a person against an infection with tubercle bacilli. This would make erythema nodosum much more important than a self-limited disease. However, critical examination of the literature and evaluation of my own patients do not allow me to accept tuberculosis as the cause of all such lesions. Nor can I agree that all cases of erythema nodosum are an initial manifestation of the development of sensitization to some allergen and that the time of the appearance of the lesions is the time that the patient is hypersensitive to the allergen.

This theory assumes that the process is one of the organism's acquiring a sensitivity and reacting by the formation of nodose lesions of the lower leg, whereas, even in those cases in which the lesions were morphologically identical to erythema

From the Department of Dermatology and Syphilology, University of Minnesota, H. E. Michelson, M.D., Director.

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nodosum and occurred during the initial phase of tuberculosis, the lesions were only a part of the primary infection. They were transient, disappearing in about the same time as the so-called idiopathic type, and, if the tuberculous infection became quiescent and later recrudesced, the nodose lesions did not recur. As a matter of fact, in young patients who had an antecedent allergy to tuberculin and had had the syndrome, including hilar adenopathy, erythema nodosum did not develop. The form of erythema nodosum which accompanies a first infection with tuberculosis must, therefore, be part of a syndrome. Although its development coincides with the development of sensitivity to tuberculin, its pathogenesis is still unknown, and to assume that it is a manifestation of allergy is to offer an entirely too easy and untenable explanation for the appearance of these erythematous nodose lesions.

If nodose lesions of the lower leg develop while a patient is receiving sulfathiazole and use of the drug is discontinued, the lesions gradually disappear, but if administration of the drug is resumed, new lesions appear. Given to a patient who already has erythema nodosum, sulfathiazole has at times caused a fresh outburst of lesions, but similar experiences with any other known infector have not been recorded so far as can be determined. When erythema nodosum is caused by a drug, the eruption is rarely confined to a few sharply defined nodose lesions; rather, there are included in the eruption erythematous blotches and papules. Moreover, the total number of lesions of the eruption do not appear in a few days as in idiopathic erythema nodosum, but new lesions continue to appear. This is in direct contrast to the idiopathic type.

Idiopathic Type.—Erythema nodosum of the idiopathic type begins suddenly and is accompanied with fever and arthralgia. The lesions are few, almost all the same age, and they go through a series of color changes. The part is restored to normal without scar formation. No cause has been found, and this type rarely recurs.

Symptomatic Type.—Symptomatic erythema nodosum is usually a macular and nodose eruption accompanying certain diseases or the ingestion of certain drugs. The lesions do not have such strict morphologic criteria, the course is variable, and recurrence under the same provocation is common. There is little in the course of the symptomatic type to make its diagnosis definite, but the very definite course, the classic lesions with accompanying pain, and the slow return to normal with the color changes of an absorbing hematoma that characterize the idiopathic type serve to distinguish the two forms.

There are no identifying characteristics for the symptomatic type which may be traced to a particular cause. However, the history of the case provides some diagnostic criteria. The nodose erythematous lesions which may be looked upon as being part of a primary tuberculous infection usually, but not always, occur in children whose reactions to tuberculin were negative before the eruption appeared and strongly positive to very small doses after its appearance. In those cases in which it was possible to ascertain this factor, the time from infection to the attack of erythema nodosum varied from three and a half to five weeks, which coincides with the development of tuberculin sensitivity.

In this syndrome fever accompanies the eruption. Hilar thickening is another important finding. Such thickening may appear either unilaterally or bilaterally about one month after infection, and in favorable cases—and most are favorable—

the nodes regress with scarring or calcification in about a year. In a few patients caseation takes place, at times complicated with meningitis, and in cases of fatal termination histologic examination has proved the presence of tuberculosis.

Diagnostic Criteria.—The important diagnostic criteria for tuberculous erythema nodosum are as follows:

1. A known source and time of infection

2. A previously negative tuberculin reaction

3. A syndrome consisting of fever, erythema nodosum, hilar thickenings, and intense tuberculin reaction

4. Regression of the skin lesions in a few weeks but persistence of the thoracic lesions.

Regardless of one's conviction about the types and causes of erythema nodosum, a search for a tuberculous origin is necessary for the protection of the patient and those in his immediate vicinity.

ERYTHEMA INDURATUM

Erythema induratum was described by Bazin in 1855, and it was then considered to be the only form that was tuberculous in origin. I feel that use of the term should be reserved for those cases in which the tuberculous origin can be proved, or those in which, though the proof is not conclusive, tuberculosis would be the most reasonable cause. The morphology, course, and pathology of this condition are so well known that they need not be reviewed; however, the pathogenesis is worthy of some comment.

The fact that a large percentage of patients having nodosities of the lower leg are female leads to speculation about the reasons persons of that sex are so often involved. Also, the fact that the term nodular vasculitis, in its broadest sense, may be applied to such lesions regardless of cause indicates that the elemental lesion and its pathology are intimately connected with the circulation. If, however, discussion is confined to erythema induratum, and it is granted that the term is reserved for tuberculous cases, it may be stated that some vital physiologic change or an important injury of the local terrain must be a precursor of the flare-up, for the tuberculosis bacilli seek a locality which for some reason favors their congregating, developing, and producing a reaction which in turn is regulated by the person's inherent resistance to tuberculosis.

Most patients with erythema induratum have a so-called chilblain or unstable circulation. Their blood vessels react in an abnormal manner to temperature changes; they nearly always have cutis marmorata, which denotes a disturbance in the ability of the terminal vessels to accommodate themselves to physical stimuli. Very likely this results in a metabolic insufficiency which affects the chemistry of the tissues in the injured area. Bommer, cited by Kalkoff,[1] surmised the formation of intermediary metabolic products, such as glycerin and acetic acid, which offer a favorable culture medium for tubercle bacilli. The nerves of the terminal blood vessels are implicated, as is the vegetative nervous system. Thus, the constitution, the stigmata of an unstable vegetative system, blood vessel enervation, unusual permeability of the blood vessels, and the inoculation with tubercle bacilli together

1. Kalkoff, K.-W.: Die Tuberkulose der Haut, Stuttgart, Georg Thieme, 1950, p. 46.

constitute conditions that favor the development of erythema induratum. By various means the individual factors may be proved, but the source of the bacilli remains to be accounted for. The nature of the lesions allows no other explanation than an endogenous source and a hematogenic dissemination of the bacilli.

A primary infection assuming the characteristics of erythema induratum does not seem possible in the light of present knowledge. As with all forms of cutaneous tuberculosis, it is often impossible to demonstrate pulmonary or other visceral lesions which may be the foci from which bacilli originate. On the other hand, although internal tuberculous adenopathies are hard to demonstrate, studies on lupus vulgaris patients given vitamin D_2 therapy have shown that latent adenitis may exist. Further, there is usually a hypersensitivity to tuberculin in patients with tuberculous adenitis which supersedes in intensity that found in other localized forms of tuberculosis.

Hypersensitivity to tuberculin is the rule in erythema induratum, much as it is in the tuberculous erythema nodosum syndrome (which includes hilar adenitis). If, then, there is no palpable adenitis and no other form of tuberculosis can be demonstrated, but there is hypersensitivity to tuberculin, it is a reasonable assumption—but only an assumption— that a latent or undemonstrable adenitis does exist. Tuberculous adenitis is often occult, for such infections remain localized. The anatomical structure of lymph nodes, with the production of lymph and its subsequent drainage into the thoracic duct or directly into the general circulation, offers an explanation for the hypersensitivity based on repeated dissemination from the breaking down of small foci in a tubeculous gland, and also may be the source of the bacilli in erythema induratum. Direct demonstration of bacilli is not often possible, nor are results of animal inoculation as frequently positive as one would wish; however, when positive, the results are conclusive evidence of tuberculosis.

In summary, the diagnosis of erythema induratum is made from the clinical findings, the tuberculin sensitivity displayed by the patient, and the appearance on microscopic examination of biopsy specimens. It must be emphasized that the condition cannot be diagnosed from the histologic observations alone, for pathologic reactions involving the subcutaneous structures may be surprisingly similar, regardless of the provocator. Any inflammation which alters the fat and frees fatty acids produces reactions which are tuberculoid in appearance.

Histologically, proved erythema induratum shows an inflammatory process made up of numerous globular or lozenge-shaped masses of infiltrate compressed into a fairly well-demarcated mass which makes up the body of the lesion. The infiltrate may be in part nonspecific and in other areas frankly tuberculoid. There are varying degrees of necrosis, and at times there is a large central mass of caseation. Stains for elastic tissue often show the outlines of blood vessels in the center of the individual foci infiltrate. In the hypoderm the trabeculae are thickened with infiltrate, and the fat is compressed or replaced with infiltrate. At times larger vessels are seen to be completely occluded with the formation of intravascular tubercles. The entire picture is that of a tuberculous inflammation.

Most cases of erythema induratum begin insidiously, but an acute onset is possible. In such cases the lesions begin as rather diffuse red plaques, not elevated but simulating erythema nodosum. Slowly the acuity subsides, and the lesions acquire characteristics which align them unequivocally with erythema induratum. The course is always chronic, with or without ulceration, and when healing finally

takes place, there is scar formation which alters the contour of the leg. Recurrences are common, in fact the rule, and even if the patient has a superficial tuberculous adenitis, which is considered to be the bacillary source, and this is clinically cured, there may be recurrences. Recurrences may be due, of course, to other sources of infection or to the fact that the adenitis has not been entirely healed and may, therefore, continue to furnish the very few bacilli that are necessary to provoke a lesion in a hypersensitive subject.

The important known facts concerning and the conditions necessary for erythema induratum are as follows:

1. A source from which the tubercle bacilli may be disseminated (either demonstrable or occult tuberculosis) must be present.

2. The patient may be predisposed to the eruption because of vascular peculiarities of the lower leg.

3. The physiologic peculiarities indicated are commoner in female patients.

4. The patient must be hypersensitive to tuberculin.

5. The histologic structure of the lesions must be tuberculoid or frankly tuberculous in type.

6. The course of the disease is chronic.

NODULAR VASCULITIS

Nodular vasculitis is a term applied to both acute and chronic nodular lesions of the lower leg which may simulate either erythema nodosum or erythema induratum but diverge sufficiently to exclude diagnosis of either of these conditions. It is almost impossible to describe or even to outline all the variations which this form manifests; nevertheless, it is a convenient and useful heading under which to classify a confusing series of inflammatory nodose lesions. Each case or group of cases so listed has its own characteristics, but in each of them some connection with the vascular network and a perivascular inflammation exist. The lesions do not meet the diagnostic criteria of erythema induratum, and an etiological agent or factor cannot be found; however, they are often so similar to erythema induratum in cell structure that the histologic observations may confuse the diagnosis.

Patients for whom a diagnosis of nodular vasculitis is made should also be examined by a physician who specializes in vascular diseases, for most of these patients will be found to have a serious vascular disturbance which has given rise to the condition.

TREATMENT

Erythema Nodosum.—Erythema nodosum in itself requires only symptomatic treatment; the concern of the therapist is the underlying condition. If the patient is a child, he should be confined to bed until the fever has subsided; if then the tuberculin test is strongly positive and a hilar adenopathy is demonstrated, the child should be kept on an antituberculosis regimen for at least a year. If fever persists and hilar thickenings increase in size, if findings suggestive of tuberculosis are found in the chest roentgenograms, or if tubercle bacilli are demonstrated in the sputum or gastric contents, the use of streptomycin may considered. It must be emphasized that not erythema nodosum but tuberculosis is being treated. To dismiss the patient when the skin lesions have disappeared is a grave mistake. The prognosis

of erythema nodosum in patients who exhibit it as part of the syndrome of a fresh infection with tuberculosis is fairly good, but by no means does its regression insure against progress of the primary disease.

Erythema Induratum.—Erythema induratum requires both general and local treatment. If there is a palpable adenitis, a biopsy should be performed, and, if tuberculosis is found, a decision must be made concerning the choice of treatment. Surgical excision or x-ray therapy, combined with use of some of the drugs which have proved of value, is usually indicated. If visceral tuberculosis exists, the therapy of choice must be based on exigencies of this disease. Vitamin D_2, paraaminosalicylic acid and amithiozone ("tibione," a sulfonamide drug), and streptomycin are useful adjuncts to treatment but are not specific.

If there is no ulceration, the use of supportive bandages is of real value for ambulant patients; if there is ulceration, local applications of streptomycin or neomycin are of some value. Treatment of erythema induratum is tedious, as treatment of all forms of tuberculosis is protracted, and the underlying cause must be constantly kept in mind.

Nodular Vasculitis.—Nodular vasculitis is always connected with some vascular disturbance, more commonly with stasis; therefore the treatment is similar to that required for stasis dermatitis and varicose ulcers. Consultation with a vascular surgeon should be insisted upon. It should be borne in mind, however, that the outcome of vein injection or ligation is not always successful even when varicose veins are present. The dense infiltrations do not always disappear after surgical treatment, and chronic edema of the entire leg may result. Bed rest, followed by application of supportive bandages or Unna gelatin casts, should be tried before any radical irreversible treatment is undertaken, and each case of nodular vasculitis should be considered individually and most painstakingly and unhurriedly evaluated.

OBSERVATIONS ON THE PHARMACOLOGIC RESPONSES OF VOERNER'S NEVUS ANEMICUS

THOMAS BUTTERWORTH, M.D.
READING, PA.
AND
COMMANDER JOHN D. WALTERS (MC), U.S.N.

NEVUS anemicus is a congenital malformation characterized by areas of varying size and shape which appear distinctly paler than the surrounding skin. Most frequently, there is a large pale area with irregular but sharply outlined borders surrounded by smaller satellite spots. The skin of the nevus appears normal in all respects except color and presents no abnormalities in tests for pain, heat and cold, and tactile discrimination. The surrounding skin is normal in color; also, there is no increase of pigmentation at the borders of the nevus. In the majority of cases the lesion is situated on the trunk, although the face and extremities are not exempt.

Rubbing of the nevus with a towel or ice or the application of heat makes it stand out clearly against hyperemic normal skin. If these procedures are carried on too long or too vigorously, the nevus also becomes erythematous, greatly diminishing the value of the tests. Pressure with a glass slide renders the area of the nevus indistinguishable from the blanched surroundings, an observation that suggests that the primary change within the nevus may be contraction of the vessels in the subpapillary venous plexus.

Diagnostic histopathologic findings in nevus anemicus do not occur. In 1944, Piorkowski [1] summarized the histologic findings that had been recorded prior to that time. He pointed out that, although Voerner claimed he had observed the regional small blood vessels diminished in number and size and the muscular coat of the arterioles missing, other authors, including Fischer, Stein, Dittrich, and Hirota, have found the skin free from abnormalities of any kind. More recently, Beerman,[2] who studied the sections from our patients, stated the impossibility of making a diagnosis of nevus anemicus on histologic grounds.

In view of the shortcomings of morphologic methods and the existing crude clinical tests, biologic methods and functional tests, as Piorkowski advocated, seem

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The opinions and assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the Naval establishment at large.

From the Department of Dermatology and Syphilology, Graduate School of Medicine, University of Pennsylvania (Herman Beerman, M.D., Chairman), and the Pennhurst State School, Spring City, Pa. (Thomas Butterworth, M.D., Consultant in Dermatology).

1. Piorkowski, F. O.: Nevus Anemicus (Voerner), Arch. Dermat. & Syph. **50**:374-377 (Dec.) 1944.

2. Beerman, H.: Personal communication to the authors.

to be necessary in the further study of this phenomenon. This report deals with certain pharmacologic responses of this type of nevus, which, though not establishing the cause of the malformation, give a better understanding of the underlying fault and possibly eliminate certain hypotheses presented in the past.

EXPERIMENTAL STUDY AND RESULTS

Interest in nevus anemicus was first aroused by the difficulty in differentiating that abnormality from achromic nevus, vitiligo, and leucoderma acquisitum centrifugum to the satisfaction of students. The application of heat, cold, and friction so often gave such conflicting results that a more exact clinical test seemed desirable. Our first investigation consisted in the injection of 0.05 cc. of histamine phosphate, 1:1,000, intradermally in the following areas: three anemic nevi, one achromic nevus, patches of vitiligo in three persons, and one site of leucoderma acquisitum centrifugum. In all patients except those having nevus anemicus, local dilatation of the blood vessels at the site of injection, a red flare, and wheal formation followed in order. In the patients with nevus anemicus, the flare failed to appear, though local dilatation of the blood vessels and wheal formation occurred. Here, then, was another means of differentiating nevus anemicus in class demonstrations.

As a simpler timesaving and easily standardized test, a small drop of histamine phosphate, 1:1,000, was placed upon the region to be tested. Using the multiple-pressure method employed in smallpox vaccination, the side of the needle point was pressed firmly and rapidly into the drop and against the skin by an up-and-down motion. Ten pressures were arbitrarily chosen for those experiments. This technique yielded the same results as the intradermal injection of histamine phosphate.

In order to find a simpler method for classroom differentiation of nevus anemicus, achromic nevus, vitiligo, and leucoderma acquisitum centrifugum and following the work of Lewis, firm strokes were made extending from normal skin through the lesions being tested to normal skin. The normal skin and all the lesions except the anemic nevi demonstrated the triple response of Lewis, red streak, flare, and wheal. In the anemic nevi, the flare was absent, although the red streak and wheal appeared (Figure).

At this time, the pedagogic interest in diagnosing nevus anemicus became submerged in a desire to explain the absence of the flare upon stroking such a lesion. In normal skin, it is conceived [3] that a firm stroke causes the liberation of a histamine-like substance (H-substance) by the deeper cells of the epidermis. This excites the cutaneous nerve terminals, with the result that impulses set up are transmitted by way of an axon reflex to the nerve endings on the arteriole, thereby causing the release of acetylcholine. This, in turn, is responsible for the arteriolar dilatation characteristic of the flare. It seemed apparent that, within the area of the nevus anemicus, either some element in this reflex mechanism was at fault or a more centrally located source of increased sympathetic tone was operative.

To rule out the latter possibility, each of the two young adult females with nevus anemicus was given 300 mg. of tetraethylammonium chloride intravenously at the

3. Dale, H. H.: Croonian Lectures on Some Chemical Factors in the Control of the Circulation, Lancet **1**:1285-1290 (June 22) 1929.

rate of 100 mg. per minute. Lyons and others [4] have shown that the administration of this drug causes a fall in blood pressure by action on the sympathetic ganglia. The resulting rise in skin temperature and blood flow suggests obliteration of vasoconstrictor tone. Since careful clinical observation of our patients revealed no drop in blood pressure or change in color of the nevi within 30 minutes following administration of the drug, this tends to eliminate the possibility of excessive centrally initiated sympathetic tone.

In considering the axon reflex leading to the flare, many places in which the arc could be broken appeared. First of all, failure to produce H-substance in the epithelial cells of the nevus might occur. Provided such an exciting stimulus were

After a firm stroke, a red streak, flare, and wheal occur in normal skin; but the flare is absent within the nevus anemicus.

given, would sufficient amounts of acetylcholine be liberated at the other end of the reflex arc? If an adequate amount of acetylcholine were discharged by the nerve endings, would its effect be overshadowed by an increased adrenergic action, or would an excessive amount of cholinesterase render it impotent? Lastly, what of the effector cells on the arterioles and their ability to function properly after suitable stimulus? In an attempt to localize the element at fault within the axon reflex, a series of experiments was undertaken.

4. Lyons, R. H.; Moe, G. K.; Neligh, R. B.; Hoobler, S. W.; Campbell, K. N.; Berry, R. L., and Rennick, B. R.: The Effects of Blockade of the Autonomic Ganglia in Man with Tetraethylammonium, Am. J. M. Sc. **213**:315-323 (March) 1947.

Endeavoring to determine whether H-substance is liberated within the nevus, firm strokes were applied (1) just outside of the border of the nevus and (2) within the nevus close to its margin. A stroke just outside the border of the nevus caused the typical triple response of Lewis, but the flare stopped short at the edge of the nevus. A stroke within the nevus close to its margin resulted in a red streak and wheal in the abnormality. The skin of the nevus beween the wheal and its margin maintained its usual pale color, but the adjacent normal skin just outside the border became erythematous. Apparently, then, H-substance is liberated within the nevus, but the impulses set up at the nerve endings fail to elicit an erythematous response within the limits of the congenital abnormality.

Another possible explanation for the failure of the flare to occur after a stroke within the nevus was an increased sympathetic "tone" at the arterioles. The first step in the study of this link of the reflex arc was the creation of an artificial nevus anemicus. Epinephrine, 1:1,000, was applied by electrophoresis in an area of approximately 5 sq. in. (32 sq. cm.). The active solution was applied to the positive pole, and 5 ma. of current was passed for five minutes. A pronounced pale area appeared beneath the active electrode in each of the two normal subjects tested. A firm stroke was then applied from normal skin through the artificial nevus anemicus to normal skin. The triple response of Lewis was noted in the normal skin; however, the flare was missing in the artificial nevus anemicus. This experiment suggested that, perhaps, the clinical picture of nevus anemicus was due to increased sympathetic tone within the vascular bed.

If the nevus anemicus is due to increased sympathetic tone, then the administration of a sympathicolytic drug should permit the acetylcholine liberated at the nerve endings after a stroke to exercise its normal physiological function. To this end, 40 mg. of S. K. F. 688-A (*N*-phenoxyisopropyl-*N*-benzyl-β-chloroethylamine hydrochloride) was given at 9 a. m., 11 a. m., and 1 p. m. to each of two patients having anemic nevi. At 1:45, a firm stroke was applied from normal skin through the nevus to normal skin. There was no flare within the nevus, though the typical triple response appeared in the normal skin.

To determine the degree of adrenolytic action during the experiment, the blood pressures of the two patients were taken immediately after the tests, after which 1 cc. of 1:1,000 epinephrine solution was given to each hypodermically. There was no increase in the blood pressure of either patient, although on a previous occasion their blood pressures had risen 16 and 20 mm. Hg, respectively, after administration of an equal amount of epinephrine. Two girls of similar age and weight showed increases in blood pressure of 30 and 12 mm. Hg, respectively, following the injection of 1 cc. of epinephrine from the same lot.

Failure of flare formation following stroking of a nevus anemicus apparently was not due to increased sympathetic tone. Could the picture of nevus anemicus, therefore, be due to a localized deficiency of acetylcholine or to an excessive amount of cholinesterase causing rapid conversion of acetylcholine to the relatively inactive choline? The latter possibility was investigated first. Since neostigmine inhibits the destruction of acetylcholine by cholinesterase, that drug was chosen for the next tests.

The two young adult females exhibiting anemic nevi were given neostigmine, 0.5 mg., intramuscularly. One hour and one hour 40 minutes later, firm strokes

were applied from normal skin through the nevi to normal skin. One week later, the experiment was repeated, with each girl receiving 1 mg. of neostigmine intramuscularly. The results were the same with both amounts of the drug. A red streak and a wheal appeared within the nevus but no flare. The normal skin exhibited the typical triple response of Lewis. This experiment seemed to show that an excessive amount of cholinesterase was not responsible for the failure of flare formation within the nevus.

If, on the other hand, there is a deficiency of acetylcholine within the nevus, one might expect that vasodilatation would follow the introduction of methacholine (mecholyl®) chloride by iontophoresis. It was established that, with our apparatus, 0.2% methacholine chloride solution applied to controls by means of a positive electrode measuring 4 sq. in. (26.7 sq. cm.) with 4 ma. of current for five minutes would produce erythema and sweating with a goose-flesh type skin in the area treated. Two young adult females were the subjects of the experiment. In accordance with the factors mentioned above, the positive electrode was applied half on normal skin and half on the nevus anemicus.

The results in the two patients were identical. After five minutes of current, erythema of the normal skin and a pale pinkness of that portion of the nevus covered by the electrode were observed. There were sweating and goose-flesh changes in both the normal and the nevoid skin. In 5 minutes, the pink color of the nevus began to fade; in addition, the customary pallor of the area was completely restored within 15 minutes. The erythema of the normal skin and the goose flesh and sweating of the area covered by the electrode persisted in marked degree for about 45 minutes, after which they gradually faded and disappeared entirely in about one hour 15 minutes. These prolonged changes were considered due to the cholinergic effect of the methacholine. The transitory pinkness of the portion of the nevus covered by the electrode was postulated to be a result of the liberation of a histamine-like substance by the passage of ions through the skin.

The introduction of methacholine into a nevus anemicus failed to produce vasodilatation but definitely caused sweating and goose flesh. The former change is a parasympathetic effect on the arterioles, the nerves apparently liberating acetylcholine for that purpose. Though the sweat glands are innervated by the sympathetic system, they respond to cholinergic drugs. The question arose whether an amount of acetylcholine adequate to activate the sweat glands within the nevus was liberated by the sympathetic fibers. To determine this, the nevi and adjacent skin of two patients were dusted with a powder containing 2% iodine in starch. The patients were then put in a heat chamber. Within 20 to 30 minutes, free sweating occurred in the nevi as well as on the normal skin; therefore it may be said that the cholinergic fibers to the sweat glands in the nevus anemicus appear to function normally.

Having thus far failed to find an explanation for the nevus anemicus, we decided next to determine the response of the effector cells of the blood vessels within the nevus anemicus to a stimulator of the parasympathetic division of the autonomic nervous system. For this purpose, we chose pilocarpine hydrochloride, a drug which acts directly upon the effector cells in the viscus innervated by the cholinergic fibers. The fact that pilocarpine produces a hyperemia in the areas where it is injected made it suitable for our studies.

The same two young adult female volunteers used in previous experiments were studied in this test. Pilocarpine hydrochloride, 1/16 grain (4 mg.), was injected subcutaneously into the nevus anemicus; an equal amount was given beneath the normal skin on the opposite side of the back. Ten minutes later, there were beneath the normal skin erythematous patches at the sites of injection. There was no change in the appearance of the nevi, but there was profuse sweating of the normal skin and nevi. At 20 minutes, the nevi were unchanged. Wheals (1.1 by 1.1 cm. and 0.7 by 1.2 cm.) surrounded by zones of erythema (6.0 by 6.0 cm. and 2.5 by 3.5 cm.) were present at the sites of the controls. Sweating continued to be profuse. One-half hour after the injections, the wheals and flares began to subside; also, the changes were gone in a little more than an hour. Sweating likewise gradually diminished. In this experiment, the effector cells of the blood vessels within the nevi failed to respond to the stimulating influence of pilocarpine.

Here, then, was the first suggestion of the fault within the nevus anemicus. Usually, the local injection of pilocarpine produces an erythema due to the direct effect of that drug upon the effector cells on the arterioles. That change was absent within the limits of the nevus anemicus. Another parasympathetic stimulant, methacholine chloride, had already been unsuccessful in producing vasodilatation within the nevus. Piorkowski [1] reported that A. Busche (1920) had failed to increase the anemia of the nevus by injecting epinephrine into it. As none of these three drugs exhibited its normal pharmacologic reaction within the nevus anemicus, the evidence suggests that the fault is at the site of action of these drugs, namely, the effector cells. Predominance of sympathetic "tone" over the parasympathetic influence may explain the characteristic pallor of the lesion.

If the fault within the nevus anemicus lies in the effector cells, would the local administration of a parasympathetic depressant, such as atropine, produce an artificial nevus anemicus? To determine this, atropine sulfate, 1/100 grain (0.6 mg.) in 5 cc. of water, was injected subcutaneously in an area of approximately 5 by 5 cm. near the angles of the scapula of two young female adults. Ten minutes later, a firm stroke was applied from normal skin through the injected area to normal skin. Results were the same in the normal and the injected areas, though the flare was somewhat smaller than that noted in these persons prior to the administration of the atropine. It also appeared that the flare subsided more rapidly than that following strokes applied without atropine.

The experiment was repeated in somewhat different form. Atropine sulfate, 1:7,500 to 1:15,000, was applied by iontophoresis to the backs of six patients with a milliamperage varying from 0.5 to 1.5 per square inch (6.45 sq. cm.) for two to eight minutes. Tests were run with the atropine sulfate applied to both the positive and the negative electrodes. In all instances, marked erythema occurred under the electrodes moistened by a solution of atropine sulfate. This vasodilatation was considered as possibly due to the liberation of a histamine-like substance by the passage of atropine through the skin. In any event, we were not successful in producing an artificial nevus anemicus by means of atropine sulfate, a parasympathetic depressant and an antagonist of acetylcholine.

An attempt was then made to produce an artificial nevus anemicus by means of another anticholinergic drug, methantheline (banthine®; β-diethylmethyl-aminoethyl-9-xanthenecarboxylate) bromide. This substance, which inhibits stimuli

at the effector organs of the parasympathetic system when administered orally was applied in 1% solution by means of iontophoresis to the backs of two young female adults. In both instances, marked, persistent erythema occurred beneath the electrodes. As with atropine sulfate, we were unable to produce an artificial nevus anemicus such as may be accomplished by the iontophoresis of epinephrine chloride.

SUMMARY

When a firm stroke is applied to a nevus anemicus, a red streak and a wheal appear; but the flare constituting the third part of the triple response of Lewis is absent. Experiments are recorded which show that, within the nevus, H-substance (histamine-like substance) appears to be liberated by the epithelial cells. Evidence points to no increase in cholinesterase at the afferent nerve endings or abnormal sympathetic tone. Methacholine (mecholyl®) chloride applied by iontophoresis failed to produce vasodilatation in the nevus, though it did cause free sweating and goose flesh. Free sweating occurs in anemic nevi in a heat cabinet. Pilocarpine hydrochloride injected subcutaneously into the nevus failed to produce erythema, though vasodilatation occurs at the site of injection of this drug beneath normal skin. On the other hand, the injection of epinephrine into a nevus anemicus fails to increase its pallor.

Methacholine, pilocarpine, and epinephrine act at the same site, namely, the effector cells. Failure of these drugs to elicit their normal pharmacologic responses within the nevus anemicus strongly suggests that the underlying fault is in the effector cells of the arterioles. Predominance of sympathetic "tone" over the parasympathetic influence may explain the characteristic pallor of the lesion.

The pharmacologic responses reported herein, while not solving the pathogenesis of nevus anemicus, point to an underlying fault and possibly eliminate certain hypotheses presented in the past.

411 Walnut St.

United States Naval Hospital, Bethesda, Md.

MIXED TUMOR OF THE LIP

EDWARD P. CAWLEY, M.D.
AND
CLAYTON E. WHEELER, M.D.
CHARLOTTESVILLE, VA.

EGGERS [1] and Hamrick and Howe [2] have written excellent monographs on mixed tumor of the lip. This communication is not an attempt to duplicate their work, but it is an endeavor to bring mixed tumor of the lip to the attention of dermatologists. We feel that such tumors may be commoner than the paucity of reported cases indicates.

REPORT OF A CASE

L. W., a 34-year-old white man, was first seen in June, 1951, because of a lesion of the right lower lip. The patient stated that the lesion had been present for approximately one year and had been slowly increasing in size. It was asymptomatic. There was no history of trauma to the lip.

Examination revealed a firm, round, smooth nodule about 1.5 cm. in diameter on the right side of the lower lip. The nodule appeared to be within the lip, was not adherent to the overlying skin or mucous membrane, and was not tender on palpation.

On June 30, 1951, a vertical incision was made through the mucous membrane overlying the nodule. The tumor was found to be well encapsulated, yellowish-white, and quite firm in consistency. It was easily removed, and the wound healed by primary union.

Microscopic examination of the specimen showed the features of a mixed tumor (Figs. 1 and 2).

COMMENT

In 1944 Hamrick and Howe [2] assembled a total of 5 cases of mixed tumor of the lower lip and 82 of the upper lip from the world's literature and from their own material. Eggers [1] suggested that the explanation for this disparity in the incidence of mixed tumors in the upper and lower lip lies in the more complicated embryological development of the upper lip.

The parotid and submaxillary glands are the commonest locations for mixed tumors [2] of salivary gland type. In addition to the salivary glands, mixed tumors of this type have been encountered in the hard and soft palates, lacrimal glands, lips, tongue, buccal mucosa, pharynx, nasal cavities, and floor of the mouth.

The clinical features of mixed tumor of the lip are worthy of note. The tumor is usually round or oval, and both the overlying skin and the mucous membrane are intact. On palpation the lesion is painless, circumscribed, movable, and usually

From the Department of Dermatology and Syphilology, University of Virginia Medical School.

1. Eggers, H. E.: Mixed Tumors of the Lip, Arch. Path. **26**:348 (July) 1938.

2. Hamrick, J. G., and Howe, J. S.: Mixed Tumor of the Lip, Arch. Path. **37-38**:143 (Feb.) 1944.

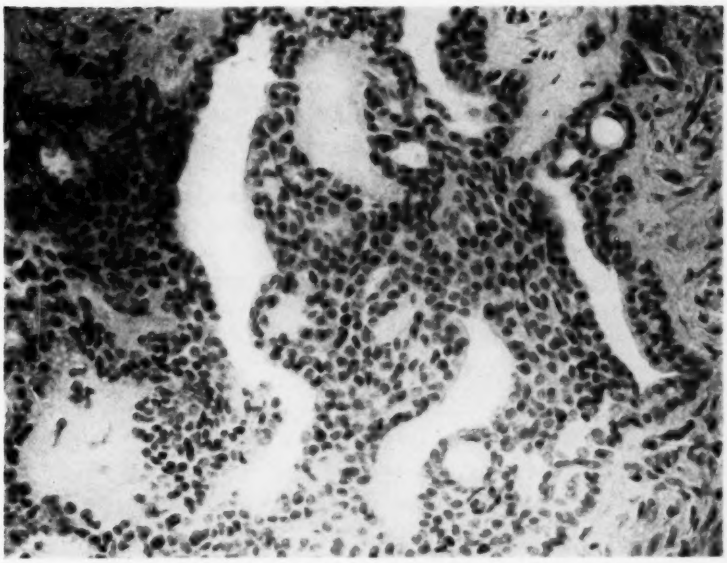

Fig. 1.—Portion of a mixed tumor of lower lip, showing glandular structures. High power.

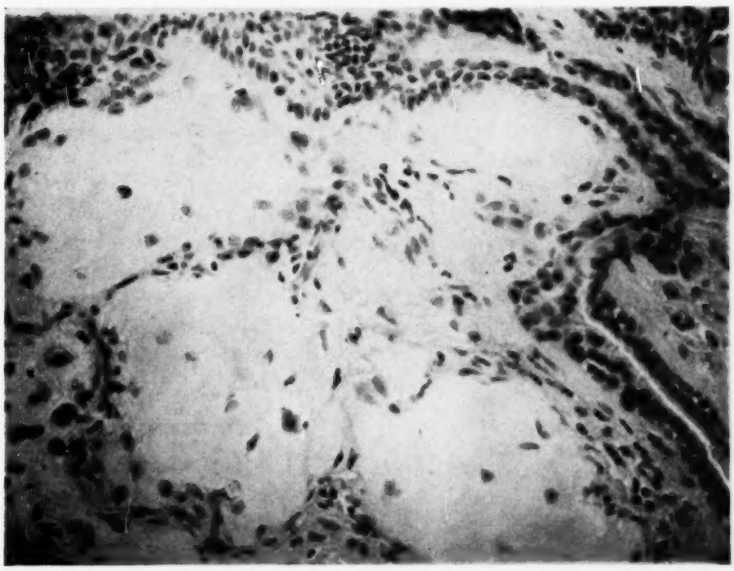

Fig. 2.—Chondroid tissue in microscopic section from a mixed tumor of lower lip. High power.

firm, but in some instances it may give the impression of being cystic. Mixed tumor of the lip must be distinguished from the common mucus-retention cyst of the lip.

Mixed tumors of the salivary gland type may vary widely in histological appearance, but they have two essential features in common wherever they occur. These are (*a*) the presence of epithelial elements and (*b*) the presence of mesoblastic elements.[3] The epithelial elements may include glandular epithelium, which is almost always present, and squamous epithelium, which is noted in the majority of cases. The mesoblastic elements may include cartilage, mucoid tissue, connective tissue, and rarely, adipose, muscle, and lymphoid tissue.[4] Ewing [5] has noted that most miscellaneous mixed tumors of salivary gland type, including those of the lip, are relatively simple histologically and that they do not duplicate the complex structure of the growths as they occur in the salivary glands.

Mixed tumors of the lip are almost invariably benign.[1] They are best treated by careful surgical excision and do not recur if completely removed.

SUMMARY

A case of mixed tumor of the lower lip is reported. We feel that mixed tumors of the lip may be commoner than the number of case reports indicates and that dermatologists should be on the lookout for them.

3. Brunschwig, A.: Mixed Tumors of the Tongue and Sublingual Gland, Surg., Gynec. & Obst. **50**:407 (Feb.) 1930.

4. McFarland, J.: Ninety Tumors of Parotid Region, in All of Which the Postoperative History Was Traced, Am. J. M. Sc. **172**:804 (Dec.) 1926.

5. Ewing, J.: Neoplastic Diseases, Ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 774; cited by Driver, J. R.: Mixed Tumor of the Palate, Arch. Dermat. & Syph. **33**:73 (Jan.) 1936.

PEMPHIGUS VEGETANS

A Clinicopathologic Correlation

WILLIAM DIRECTOR, M.D.
NEW YORK

IN PEMPHIGUS vegetans, in contradistinction to pemphigus vulgaris, there is close agreement concerning histologic changes. These are acanthosis and papillomatosis involving predominantly the rete pegs (ridges) and microabscesses within the hyperplastic rete pegs containing large numbers of eosinophiles. I cite a few representative opinions without attempting to review all sources. Montgomery and co-workers [1] state that the histologic changes of pemphigus vegetans are quite distinctive and may occur at any level of the epidermis. Ormsby and Montgomery [2] are in general agreement, adding that eosinophiles also predominate in the papillae and that there is a resemblance to blastomycosis and bromoderma. Lever [3] agrees and mentions that early there is low-level acantholysis as in Darier's disease (keratosis follicularis) but without dyskeratosis; that older lesions show no bullae but only acanthosis and papillomatosis resembling pseudoepitheliomatous hyperplasia, while the intraepidermal abscesses resemble bromoderma and pyogenic granuloma. Civatte,[4] also in general agreement, states that the initial bulla is that of typical pemphigus vulgaris and that later in the acanthotic lesion there is splitting as if the bulla of pemphigus vulgaris is again re-forming.

The study of biopsy specimens from eight cases of pemphigus vegetans has led me to agree with the general opinion about the histologic changes. The patients were observed during the past five years, and several biopsies were performed at different times in the same patients. In a few instances a bulla was included in addition to the vegetative papule. In one instance dry papules were removed at two different occasions. Many sections of each biopsy block were studied in series.

As in pemphigus vulgaris, I find myself in closest agreement with the opinion of Civatte in that the early bullous lesions show the characteristic changes of pemphigus vulgaris, namely, an intraepidermal bulla produced by acantholysis at or close to the suprabasal level. My interpretation of pemphigus vegetans is that it

From the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School (Dr. Marion B. Sulzberger, Chairman) and the Service of Dermatology and Syphilology of Bellevue Hospital (Dr. Frank C. Combes, Chief of Service).

1. Montgomery, H., and others: Atlas of Dermal Pathology, Washington, D. C., Registry Press, under the Auspices of the National Research Council, Army Institute of Pathology, 1948, p. 69.

2. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Ed. 7, Philadelphia, Lea & Febiger, 1948.

3. Lever, W. F.: Histopathology of the Skin, Philadelphia, J. B. Lippincott Company, 1949.

4. Darier, J.; Civatte, A., and Tzanck, A.: Précis de dermatologie, revised by A. Civatte, Ed. 5, Paris, Masson & Cie, 1947.

is merely a reactive phase of the patient with pemphigus in the direction of increased resistance to the disease. This phase may be of variable duration and may not prolong the life of the victim beyond the usual range in pemphigus vulgaris. This phase may alternate with the frank bullous stage or coexist with it. In some patients it becomes the dominant phase and really extends the life of the sufferer far beyond the usual duration of pemphigus vulgaris. As such it really results in a partial and temporary victory of the host over the disease.

The visible mechanism whereby this is achieved is hyperplasia of the epidermis. This in part prevents dissolution of the skin which occurs in the bullous phase. When acantholysis does occur in the hyperplastic epidermis, the greater thickness and coherence of the resistant prickle cells prevent the clefts from expanding into bullae which rupture, resulting in the loss of fluid, protein, and salts as the residual epidermis of the bullae floors erodes to leave exposed corium.

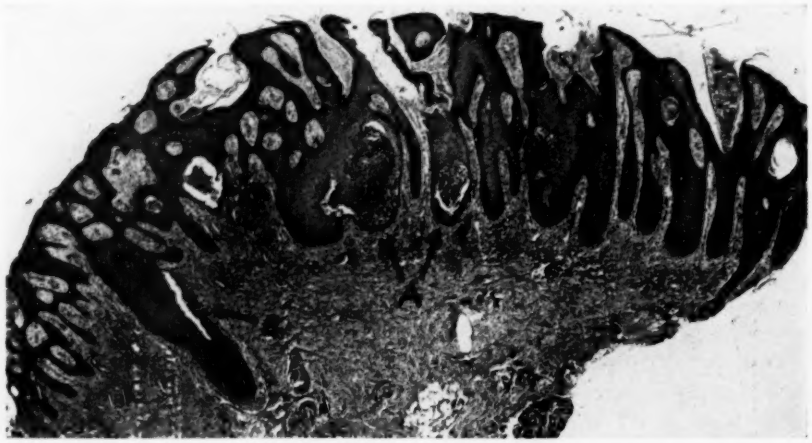

Fig. 1 (Patient J. C.).—Typical features of pemphigus vegetans: acanthosis and papillomatosis, intraepidermal abscess containing eosinophiles and neutrophiles marked by arrows at *A*. Arrow *B* points to splitting in a hyperplastic rete peg, resulting in a cleft analogous to the cavity of a bulla of pemphigus vulgaris. × 85.

Nevertheless, the fundamental pathologic changes which take place in pemphigus vegetans are in essence those of pemphigus vulgaris and consist in cleavage of the hyperplastic epidermis at a low level, frequently at or close to the suprabasal level, and consequent inflammatory reaction. Regrowth of the hyperplastic epidermis smothers the effects of the acantholysis by pushing upward the cleft areas, giving rise to intraepidermal abscesses through the entry of inflammatory cells.

The hyperplasia or acanthosis is irregular and variable, ranging from moderate to massive. The reaction occurs predominantly in the rete pegs (ridges), some of which may remain discrete while others undergo bridging and fusion with neighbors to form thick masses or an irregular retiform pattern. The surface may be thrown up in irregular papillations, the intervening troughs becoming filled with a mixture of keratin and parakeratotic scale, as well as the contents of shedding microabscesses. No specific degenerative cellular changes are discernible with the staining methods employed at present. Both intercellular and intracellular edema may occur among

the prickle cells but is not remarkable. Inflammatory cells, eosinophiles, neutrophiles, and lymphocytes are at times found traversing the rete pegs containing the microabscesses.

The microabscesses contained within the acanthotic rete pegs are entirely analogous to the cavities of the bullae of pemphigus vulgaris. They appear at varying levels up to the surface. The mechanism of their production is as follows: The earliest change is splitting at, or somewhat above, the suprabasal layer. This may be quite irregular, occur not only toward the bottom of the peg but also in the wall at any level, and curve around in irregular planes. These clefts or potential bulla cavities initially contain few or no inflammatory cells but only a few epidermal

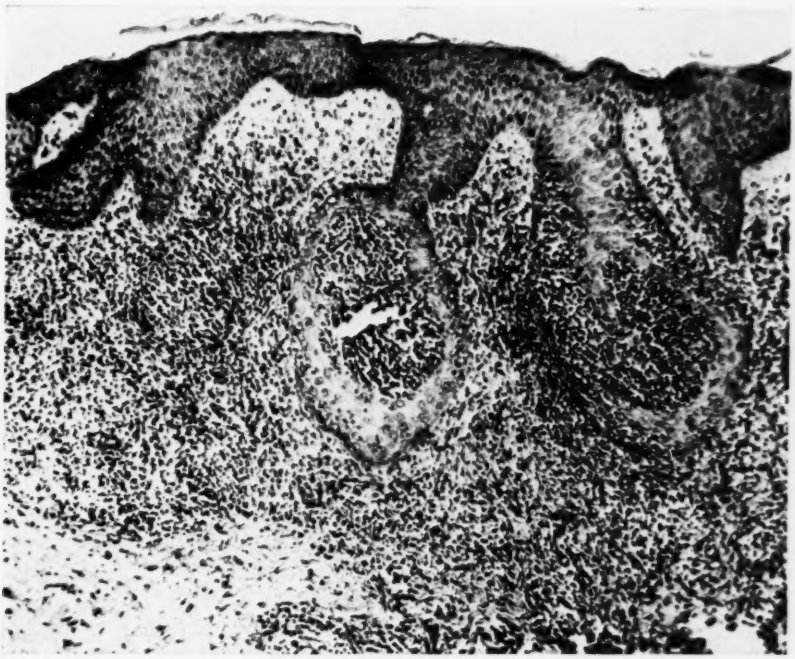

Fig. 2 (Patient A. M.).—Characteristic eosinophile abscesses within acanthotic rete pegs. Surrounding upper corium contains diffuse relatively dense infiltrate with a large proportion of eosinophiles. × 115.

cells liberated singly or in clumps. Inflammatory cells and fluid then pass through the epidermal walls into the clefts, expanding and rounding them to yield characteristic microabscesses. In different biopsy specimens or sections of the same biopsy specimen either of these two stages may predominate or both may coexist in varying ratio.

Regrowth of the epidermis around and below the abscess cavities pushes them upward to the surface, where they are shed. This accounts for the varying levels of the microabscesses within the rete pegs and is analogous to the healing of a pemphigus bulla by regrowth of the epidermal floor. In older abscesses the inner-

most epidermal cells which line the cavity become flattened and may show to some degree the presence of granular layer formation. This also is similar to the appearance of the granular layer in the regenerating epidermis of the floor of a bulla of pemphigus vulgaris in the healing stage.

Another feature occasionally seen is analogous to the secondary cleavage in the regenerating epidermal floor of the pemphigus bulla which gives rise to the picture of "bulla under bulla." This consists in multiple abscesses within a single rete peg. These may be of equal or unequal size. Some larger abscesses appear multilocular due to the presence of irregular strands of prickle cells which traverse the abscess

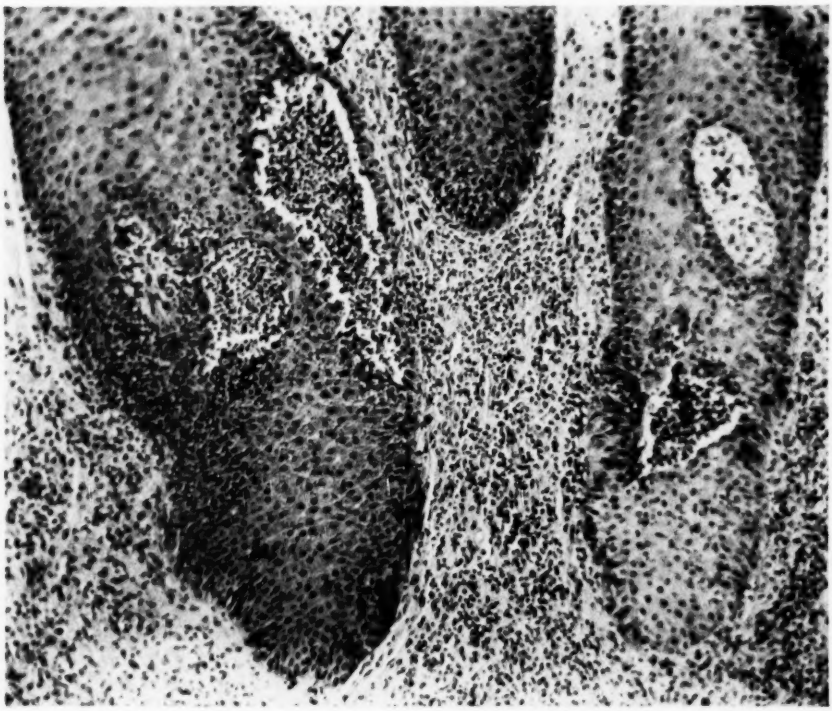

Fig. 3 (Patient F. P.).—Lower portions of two acanthotic rete pegs showing small abscesses at varying levels. Arrow points to abscess pocket formed by suprabasal acantholysis toward side of peg. Portions of corium included within rete pegs by irregular bridging and fusion are marked by *X*. × 126.

and separate it into pockets of varying size. This is apparently produced by differing levels of acantholysis at the same or different times with evolution into abscesses. Another slight variation in structure is a retiform pattern of bridging acanthosis with acantholysis in the lower portion and formation of small irregular intraepidermal bullae rather than microabscesses.

When the vegetative phase undergoes involution, small dry papules may replace the larger moist and crusted ones; these may persist for weeks or months. In one patient during a regressive stage, large clusters of such sessile and pedunculated

papules reached a split-pea size. Such papules and nodules revealed only acanthosis, without sign of splitting at any level. In the vegetative papule which shows the characteristic cleavage and microabscesses there occur, also interspersed among the others, many rete pegs in which only acanthosis is present. The ratio of intact to cleft acanthotic pegs may vary considerably. Maintenance of the integrity of intercellular cytoplasmic processes appears to be the microscopic evidence of this resistant phase of pemphigus.

The inflammatory reaction takes place in the papillary and upper portion of the corium. Edema and vasodilatation may vary considerably. The infiltrate also

Fig. 4 (Patient M. Z.).—Stages in evolution of intraepidermic abscesses are illustrated in one area. Near surface is old abscess which has been pushed upward by growth of epidermis. Arrow *A* points to focus of re-formed granular cells around abscess. Arrow *B* indicates fresh suprabasal cleft, the start of a new abscess. *X* marks an inclusion of corium. × 153.

varies in number and variety of cells. In addition to lymphocytes and histiocytes, neutrophiles and eosinophiles are almost always present in varying ratios. While eosinophilia is common, neutrophiles may occasionally be the predominant cell in the clefts or microabscesses. The presence of eosinophiles in the microabscess is not invariable. Plasma cells may occasionally appear, as may melanophores in deeply pigmented skin. Blood monocytes are very difficult if not impossible to differentiate in fixed tissue sections, especially among the inflammatory cells in bullae or microabscesses. The zone of edema and infiltration is usually deeper than in lesions of pemphigus vulgaris.

Clinically there is also agreement that pemphigus vegetans is manifested in the beginning by bullae which appear first on the mucosae or skin; that sooner or later the eroded lesions become vegetative; that remissions and exacerbations occur over a period of years (6 to 12 according to Darier, Civatte, and Tzanck [4]); that the outcome is fatal in the large majority, but also that there are cases with a short fatal course, a matter of a few months.

My series of eight cases follows this general picture and displays a wide range of clinical features. At one extreme they merge with pemphigus vulgaris in respect

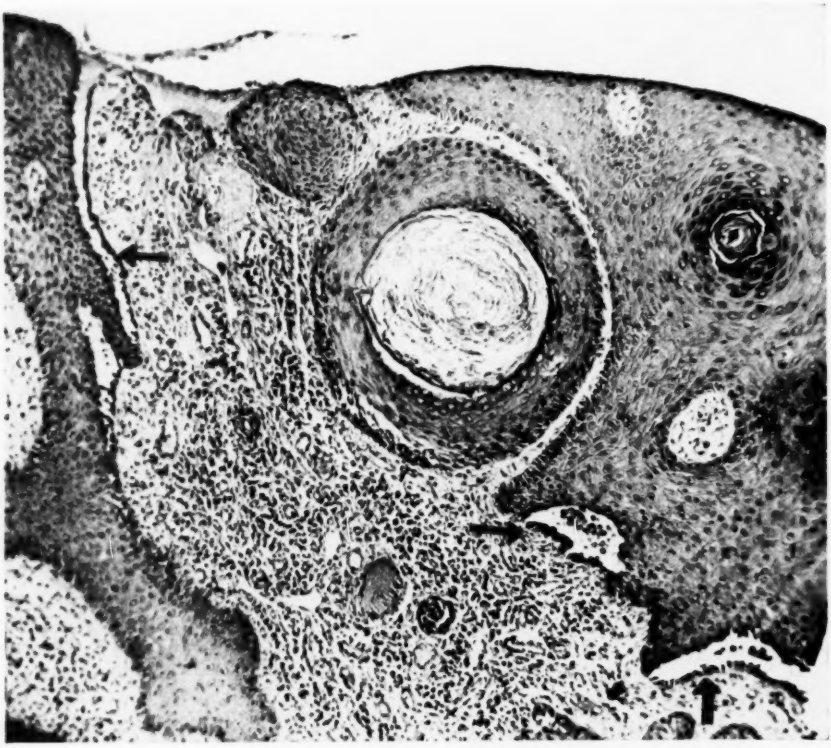

Fig. 5 (Patient D. B.).—Moist abraded vegetation showing irregular acanthosis with dilated comedo-like follicle orifice. Typical abscesses are not present. Arrows point to suprabasal acantholysis at sides and bottom of hyperplastic rete pegs. Central arrow points to tiny cleft containing only free prickle cells. Both features, minus acanthosis, are characteristic of bulla of pemphigus vulgaris. × 115.

to a short course before fatal termination usually in the bullous stage, mode of onset, and periods of alternation between bullous and vegetative stages as well as concomitance. These resemble cases of pemphigus vulgaris in which for varying periods there appear small vegetative papules scattered about or grouped in the flexures. At the other extreme are cases which after a bullous onset soon become vegetative and so remain, with long duration and periods of complete or partial

remission. In between are cases which at the onset and for some time thereafter are bullous but later become predominantly vegetative, although there may be an occasional shower of bullae. Such cases also have a long duration.

Of the eight cases, three fell into the first group which essentially followed the course of pemphigus vulgaris but in which bullous and vegetative stages fluctuated and overlapped. The outcome was fatal during a predominantly bullous phase, the duration lying approximately within the range of that of pemphigus vulgaris. The patients included a woman of 58 years who died about 9 months after blisters appeared in the mouth and on the scalp; a man of 54 years who died 6½ months

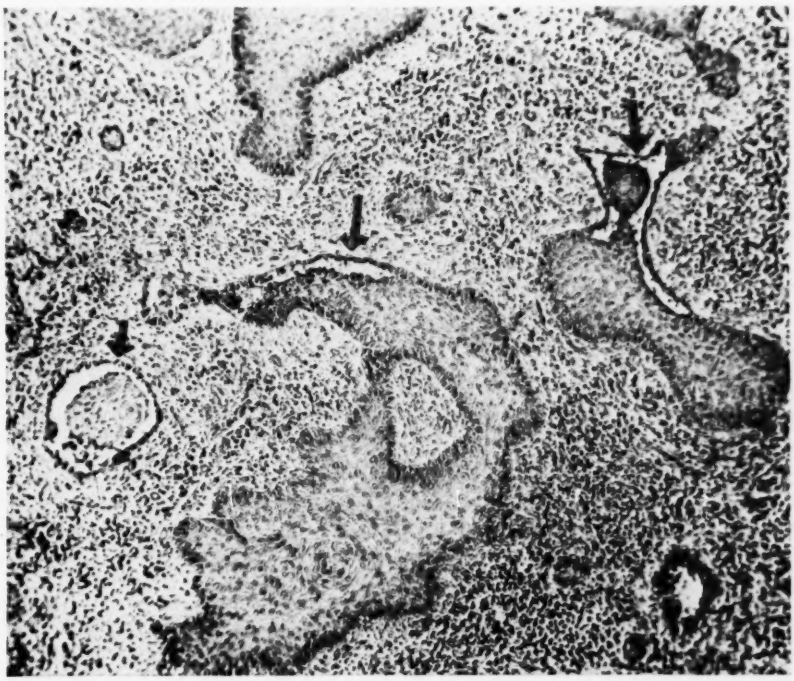

Fig. 6 (Patient D. B.).—Same biopsy specimen as Figure 5. Transverse sections with arrows pointing to foci of suprabasal cleavage in irregular cross sections of acanthotic pegs. Suprabasal level is clearly and sharply maintained despite irregularly curving planes of cleavage. × 115.

following the outbreak of bullae in the mouth, and another 54-year-old man who died two years after the disease began but who had only oral lesions for the first 18 months. An autopsy performed on the third patient disclosed bronchopneumonia, fatty change of the liver, hyperplasia of the bone marrow, and chronic lymphadenitis of both axillae. There were no pathologic changes in the adrenal glands, and bullae were not found in the bladder or gastrointestinal tract.

The remaining five cases fell into the intermediate and predominantly vegetative groups. At the time of writing four patients were still alive two to five years after

the onset of their disease. One was an unusual case, that of a 42-year-old man who died about 17 months after the outbreak of bullae in the mouth and two weeks later on the skin. This first attack lasted two and a half months and was bullous only. After a short remission, a second attack ensued, which became predominantly vegetative and lasted several months. During the final five and a half months of life he had no cutaneous or mucosal lesions. Prior to and during the attacks of pemphigus the patient had symptoms of a hepatorenal syndrome and portal cirrhosis, verified by a liver biopsy. He died shortly after this operation. Also in this group was a 71-year-old woman whose disease began more than five years before, with itching and bullae on the labia majora and in the groins. The lesions became generalized and three months later entered the vegetative stage. The disease

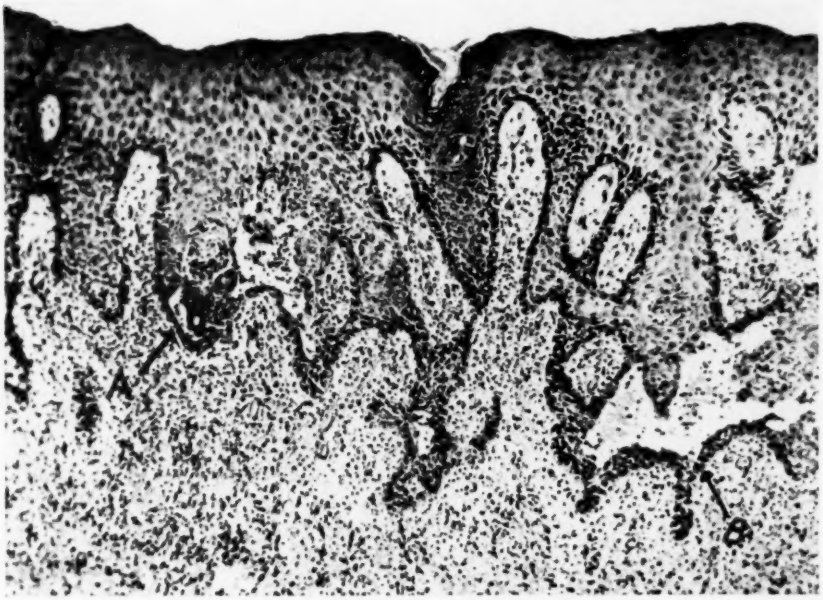

Fig. 7 (Patient M. H.).—Another histologic variant of pemphigus vegetans, indicating transition from pemphigus vulgaris: retiform pattern of bridging acanthosis with intraepidermic abscess (arrow *A*) and suprabasal acantholysis (arrow *B*) in lower portion of epidermis. × 115.

remained active for three years. During the past two years there have been no lesions of the skin or mucosae other than some areas of depigmentation.

The age of the patients when the disease began varied from 42 to 70 years, seven cases occurring in the fifth and sixth decades. There were three women and five men. All the patients exhibited bullae as the earliest sign of the disease; in four these appeared first in the mouth, in two on the skin; two had bullae on both the skin and the mucosae (mouth and scalp, labia majora and groins). However, all patients had oral as well as cutaneous bullae at one time or other. Blepharoconjunctivitis occurred in two patients, at the onset in one and later in the other. The interval between mucosal and cutaneous bullae or the reverse was two to four months

in seven cases; in one fatal case mouth lesions alone were present for 18 months prior to the eruption of cutaneous blisters. The interval between the onset of the disease and the appearance of vegetative lesions varied from one to nine months, in seven cases lying between one and four months.

As in pemphigus vulgaris, laboratory examinations showed no specific or characteristic changes. Secondary anemia and depressed total serum proteins, with occasional reversal of the albumin-globulin ratio, occurred during the height of disease activity. Blood eosinophilia was present in seven cases and absent in one. The eosinophiles varied from normal to 38%, were low in three, high in four, but

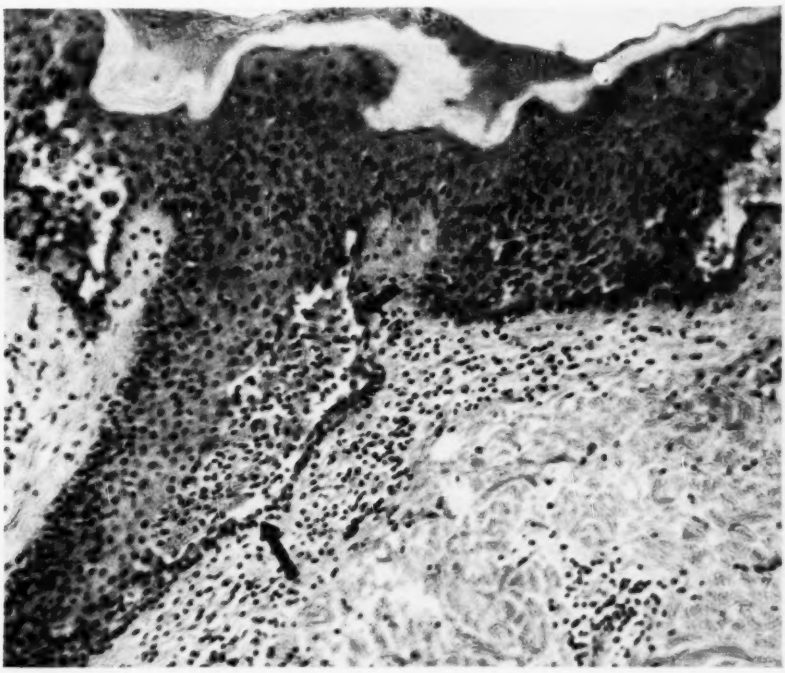

Fig. 8 (Patient J. D.).—Case of pemphigus vulgaris with typical small bullae appearing at edges. Central pilosebaceous follicle contains in its wall a microabscess such as occurs in pemphigus vegetans. This is another histologic instance of overlap between these two stages of pemphigus. × 170.

persistently high in only one case (20 to 38%). So far as the tissues were concerned, eosinophilia was present in the vegetative lesions of seven patients, including the two biopsy specimens of dried papules, and was absent in one biopsy specimen. In the four instances of a bulla biopsy, two showed the presence of many eosinophiles, in one they were scanty, and in the fourth were absent. In two biopsy specimens there was eosinophilia of both bulla and vegetation; in one there was esoinophilia of the bulla but not of the vegetative papule; in the fourth the reverse was the case. Thus, while eosinophilia of the blood and cutaneous lesions occurred in the large majority of cases, it was not invariable, and coordination among them was not always present.

However, no conclusions were drawn since blood counts and biopsies were not performed simultaneously or even on the same days.

CONCLUSIONS

The histologic structure of the lesions of pemphigus vegetans is characteristic and in conjunction with the clinical picture is fairly diagnostic. It is basically that of pemphigus vulgaris, acantholysis at a low level of the epidermis, but modified by hyperplasia of the epidermis and its subsequent cleavage.

Pemphigus vegetans represents a phase of relative resistance to the disease as is indicated by the longer duration as compared with pemphigus vulgaris and is reflected in the hyperplastic reaction of the epidermis.

With clinical regression dry papules can replace the moist vegetations; these reveal acanthosis only. It, therefore, appears that increased resistance to the disease is accompanied with increased resistance to rupture on the part of the intercellular bridges of the epidermal cells.

TUMOR-LIKE KERATOSES

Report of a Case

MAURICE T. FLIEGELMAN, M.D.
AND
ADOLPH B. LOVEMAN, M.D.
LOUISVILLE

THE DEVELOPMENT of tumors on the dorsa of the hands in a patient following a severe sunburn was first reported by Poth [1] in 1939. Spontaneous involution occurred in approximately eight months. Two previous similar experiences had been noted by this same patient.

In his paper Poth adequately reviewed the literature of actinic dermatoses, and Stillians,[2] in 1950, presented additional data on the effects of irradiation of the skin.

The following case is presented in some detail because Poth [3] feels that it is the first case since his original report that parallels his case both clinically and histologically.

REPORT OF CASE

Mr. D. L. C., aged 75, was referred to the dermatology clinic of the Veterans Administration Hospital, Louisville, in February, 1950, because of multiple warty growths on the dorsa of his hands and wrists.

The patient had been a blacksmith from 1923 to 1943, and in 1942 he first noted a rough, warty growth on the dorsum of his left hand. Shortly thereafter several others developed. He was uncertain about the presence of lesions on the right hand at this time. He was right-handed; thus, his left hand was constantly closer to the fire and the hot anvil. According to the patient, all the lesions disappeared spontaneously after several months.

In 1944 he started working for the Kentucky State Highway Department, much of his work being outside. This occasionally involved supervision of men putting tar on roads, although he never actually handled the tar himself. In 1948, in his spare time, he did some blacksmithing, and again a warty growth developed on the back of his left hand which regressed of its own accord in several months. He could not recall, however, whether there were similar lesions on the right hand at that time.

From the Medical Service, Veterans Administration Hospital, and the Department of Dermatology and Syphilology of the University of Louisville School of Medicine.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Poth, D. O.: Tumor-Like Keratoses: Report of a Case, Arch. Dermat. & Syph. **39**:228-238 (Feb.) 1939.

2. Stillians, A. W.: By-Effects of Irradiation of the Skin, J. A. M. A. **114**:743 (Oct. 28) 1950.

3. Poth, D. O.: Personal communication to the authors.

Fig. 1.—Dorsa of hands at height of eruption in February, 1951. Note bilateral distribution, hyperkeratotic appearance, and clinical resemblance of some lesions to squamous-cell carcinoma.

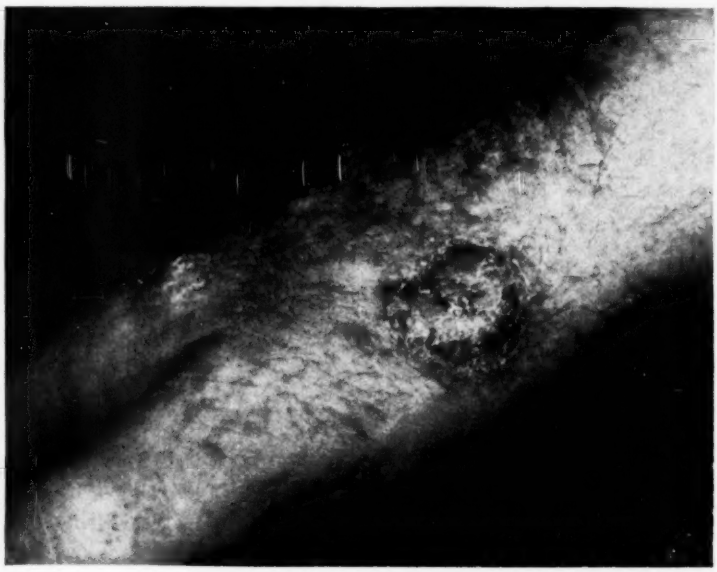

Fig. 2.—Dorsum of right hand at height of eruption in February, 1951.

During the summer of 1949, while out of doors and on his feet much of the time, he had pruritus, erythema, and edema of his ankles for the first time, for which he was hospitalized. A diagnosis of peripheral vascular insufficiency was made. At the same time that his ankle edema developed he noted the slow growth of numerous warty, tumor-like lesions over the dorsum of each hand and wrist. These were asymptomatic.

Cutaneous examination, in February, 1950, showed 4 tumors on the dorsum of the left hand and 12 or 13 on the dorsum of the right hand and wrist. These varied from 0.5 to 2 cm. in diameter and height. They were all roughly circular and firm, and several had a pearly appearance. Several had umbilicated centers, a few were crusted, but most of them showed fairly thick scaling. None appeared on an inflammatory base. There was no regional adenopathy (Figs. 1 and 2).

Fig. 3.—Spontaneous involution of lesions occurring in April, 1950 (two months after Figures 1 and 2).

The differential diagnoses included squamous-cell carcinoma, unusual verruca vulgaris, or possible nodular neurodermatitis. The ward surgeon had instituted treatment with potassium permanganate soaks and calamine lotion, with no apparent change in the lesions.

When the patient was seen in the dermatology clinic, a biopsy of one of the lesions was done. Pending this report, and with the remote possibility of a nodular neurodermite in mind, an occlusive dressing of 3% ichthammol ("ichthyol") paste was placed on one hand for one week. No change was noted at the end of that time. It was then that a clinical diagnosis of Poth's tumor-like keratoses was first considered and all treatment stopped.

Subsequent Course.—By April 25, 1950, there was noted a gradual involution of all the lesions (Fig. 3). A few were cystic, and, upon incising them, sebaceous-like material was easily expressed. This feature has not been described previously.

On one visit, in July, 1950, the patient complained of some tenderness in one of two of the larger lesions, from which sebaceous-like matter could still be expressed.

Spontaneous regression of the lesions continued throughout 1950. By April 16, 1951, all of them had completely disappeared. The largest lesions left superficial, white, atrophic, "reticulated" scars, whereas the smaller ones left none.

We had planned to expose this man to further actinic rays in an attempt to reproduce the keratoses, but, unfortunately, the day after our last examination he died of a coronary occlusion (April 17, 1951).

Laboratory Data.—Complete blood count and results of urinalysis on two occasions were within normal limits. The Kahn test was negative.

The biopsy specimen (Fig. 4) was taken from one of the larger lesions. The histologic observations were as follows: There was a narrow layer of parakeratosis. The epidermis

Fig. 4.—Biopsy section of one of larger lesions (× 78) showing parakeratosis, acanthosis, and pseudoepitheliomatous hyperplasia. Some deeper rete pegs show horny plugs or cysts. Bands of epithelial cells stream from overlying epidermis, and, while epithelial proliferation is atypical, degree of activity does not suggest carcinoma. Marked cellular infiltrate extending among sweat glands and into subdermal fatty tissue consists of lymphocytes, eosinophiles, and large mononuclear cells.

beneath showed a few atrophic areas, but in general there were a moderate to a pronounced acanthosis and pseudoepitheliomatous hyperplasia. The deeper rete pegs showed horny plugs or cysts. Some of the cornified areas were much larger than those usually seen. Several detached islands of mature squamous cells which probably represented tips of adjacent pegs were noted. Bands of epithelial cells could be seen streaming from the overlying epithelial tissue. While the epithelial proliferation was atypical, the degree of activity in no way suggested carcinoma.

There was a marked cellular infiltrate of lymphocytes, eosinophiles, and large mononuclear cells, probably histiocytes. The infiltrate extended among the sweat glands and into the subdermal fatty tissue.

COMMENT

The clinical course and histological observations in our patient closely parallel those described by Poth.[1]

Although a clinical diagnosis of squamous-cell carcinoma was one of those originally entertained and the biopsy section might have been interpreted as such, closer inspection militates against such a diagnosis. The regular pattern of acanthosis, the few mitotic figures, the absence of invasion of the underlying tissue, and other features nullify such a diagnosis.

The spontaneous involution of all lesions without treatment was noted.

An occasional case of epithelioma which healed without treatment has been reported, the most recent of which was presented at the Los Angeles Dermatological Society.[4] However, frequently, as in this case, the clinical and histologic features are scantily presented, and the conclusions are not clear-cut.

CONCLUSIONS

An additional case of tumor-like keratoses on the dorsa of the hands is reported. The first was described by Poth in 1939.

The distinctive features of this disease are its presentation of a definite clinical and microscopic resemblance to squamous-cell carcinoma and its spontaneous involution without treatment.

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4. Ayres, S., Jr.: Squamous Cell Epithelioma (Self-Healing Type), Arch. Dermat. & Syph. **58**:584 (Nov.) 1948.

DIETHYLSTILBESTROL IN THE TREATMENT OF SENILE SEBACEOUS ADENOMA

WALTER C. LOBITZ Jr., M.D.
AND
DONALD P. COLE, M.D.
HANOVER, N. H.

IT HAS been shown by Miescher and Schönberg [1] that the ratio of sebaceous gland secretion to sebaceous gland area in a given area of the skin is constant. In other words, the amount of sebaceous gland secretion is dependent on the size and number of sebaceous glands only; any substance which increases (or decreases) the sebaceous gland secretion does so by increasing (or decreasing) the size of the sebaceous gland.

Basic evidence is accumulating to indicate that the androgens and the estrogens when given internally or applied topically influence the size of the sebaceous gland in laboratory animals as well as in human beings.

Androgens (for example, testosterone propionate) cause an increase in the size of the sebaceous gland, as was shown by the studies of Hamilton [2] and Rony and Zakon [3] with human subjects, and by Montagna and Kenyon [4] and Hamilton and Montagna [5] with laboratory animals.

On the other hand, estrogens (for example, diethylstilbestrol) effect a decrease in the size and number of the sebaceous glands, as was shown by the studies of Rony and Zakon [3b] and Eller and Eller [6] with human subjects, and by Hooker and Pfeiffer [7]

From the Department of Dermatology, Hitchcock Clinic and Dartmouth Medical School (Dr. Lobitz). Dr. Cole is Fellow in Dermatology, Dartmouth Medical School.

1. Miescher, G., and Schönberg, A.: Untersuchungen über die Funktion der Talgdrüsen, Bull. schweiz. Akad. med. Wissensch. **1**:101, 1944.

2. Hamilton, J. B.: Male Hormone Substance: Prime Factor in Acne, J. Clin. Endocrinol. **1**:570 (July) 1941.

3. Rony, H. R., and Zakon, S. J.: (*a*) Effect of Androgen on the Sebaceous Glands of Human Skin, Arch. Dermat. & Syph. **48**:601 (Dec.) 1943; (*b*) Effect of Endocrine Substances on the Adult Human Scalp, ibid. **52**:323 (Nov.-Dec.) 1945.

4. Montagna, W., and Kenyon, P.: Growth Potentials and Mitotic Division in the Sebaceous Glands of the Rabbit, Anat. Rec. **103**:365 (March) 1949. Montagna, W.; Kenyon, P., and Hamilton, J. B.: Mitotic Activity in the Epidermis of the Rabbit Stimulated with Local Applications of Testosterone Propionate, J. Exper. Zool. **110**:379 (April) 1949.

5. Hamilton, J. B., and Montagna, W.: The Sebaceous Glands of the Hamster: I. Morphological Effects of Androgens on Integumentary Structures, Am. J. Anat. **86**:191 (March) 1950.

6. Eller, J. J., and Eller, W. D.: Estrogenic Ointments: Cutaneous Effects of Topical Application of Natural Estrogens, with Report of 321 Biopsies, Arch. Dermat. & Syph. **59**:449 (April) 1949.

7. Hooker, C. W., and Pfeiffer, C. A.: Effects of Sex Hormones upon Body Growth, Skin, Hair, and Sebaceous Glands in the Rat, Endocrinology **32**:69 (Jan.) 1943.

and Reiss and Gellis [8] with laboratory animals. An opportunity to observe the clinical effect of systemic estrogen therapy upon the size and activity of sebaceous glands occurred when the following patient with multiple tumors of senile sebaceous adenoma presented himself for therapy (Fig. 1).

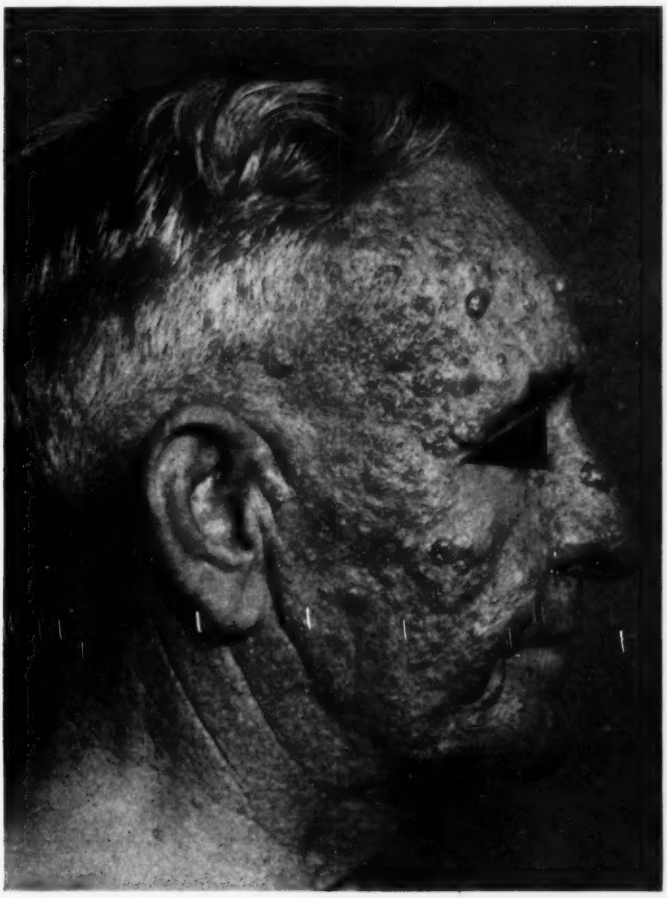


Fig. 1.—Patient before onset of therapy.

REPORT OF A CASE

History.—W. B., a white man aged 62 years, had had oily skin with prominent sebaceous gland openings and comedones since puberty. At about the age of 45 years, there began a gradual increase in the number and size of cystic and tumor-like lesions on the face and anterior chest. Cheesy material could be expressed from some of these lesions. From the time he was

8. Reiss, F., and Gellis, S.: Effects Produced on Pilosebaceous system and Adrenals of the Rabbit by Inunction of Sex Hormones, J. Invest. Dermat. **12**:159 (March) 1949.

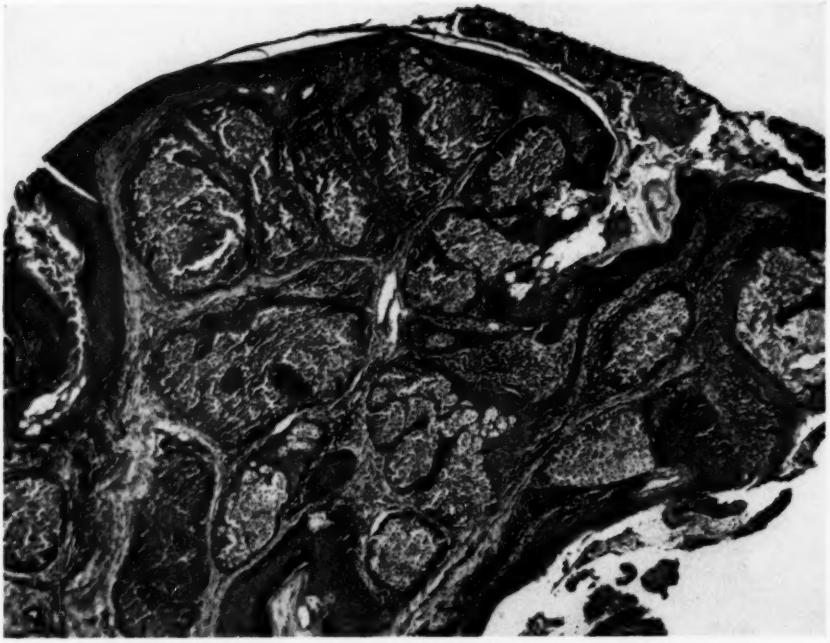
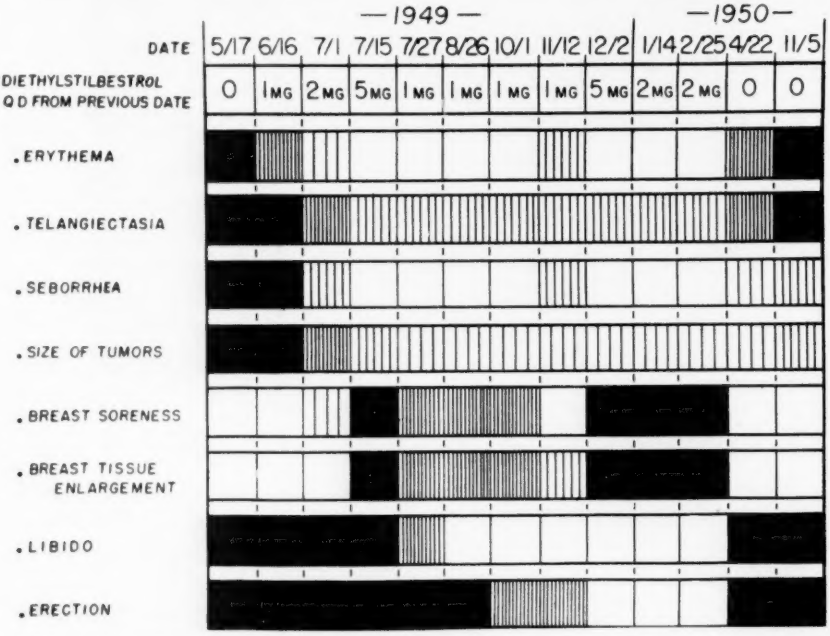


Fig. 2.—Section of a punch-type biopsy specimen taken from one tumor on the forehead. Hematoxylin and eosin stain; × 57.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. SIZE OF TUMORS
. BREAST SORENESS
. BREAST TISSUE ENLARGEMENT
. LIBIDO
. ERECTION

Fig. 3.—Diagrammatic representation of clinical course of the disease. The closer together the vertical shading lines are, the more intense the reaction. The black represents the severest degree of involvement; the white, an absence of involvement. *Q. D.* means every day.

55 years old, his wife had to change his pillow slip each morning because it was stained with a yellow oil from his face.

The patient's father and paternal grandmother had had lesions similar to those of the patient during the same age period.

The general medical history and results of general physical examination were entirely normal.

Cutaneous Examination.—Markedly oily skin, dilated sebaceous gland openings, comedones, raised tumors with single or multiple sebaceous gland openings umbilicated on their surfaces,

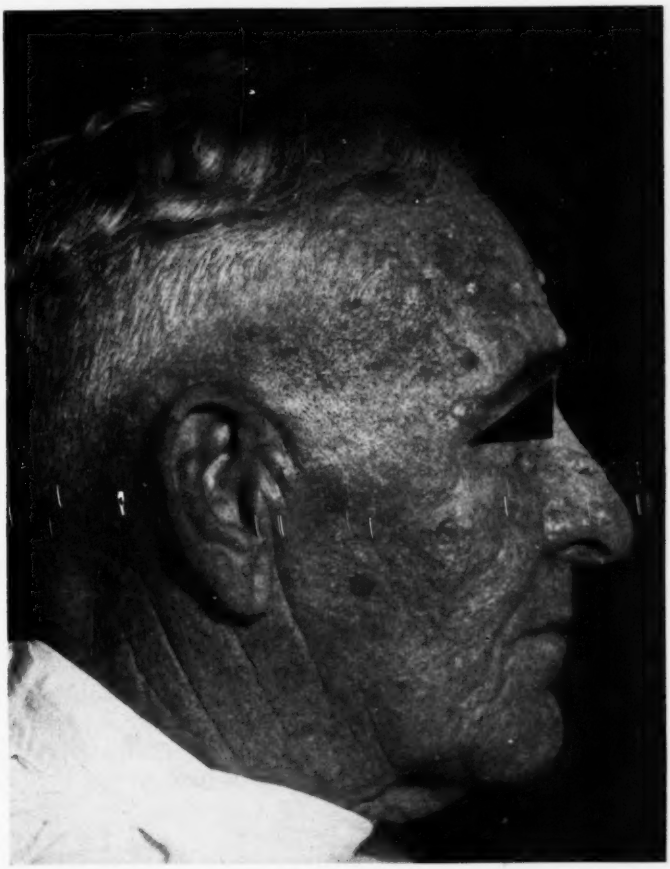

Fig. 4.—Patient on Aug. 26, 1949.

mild erythema, and telangiectasia were all present on the face, neck, upper chest, and back. The hair type and distribution, body build, fat distribution, primary and secondary sexual characteristics, etc., were within normal physiological limits. A biopsy was performed (Fig. 2).

Course.—The only treatment that the patient received was diethylstilbestrol by mouth. The chart (Fig. 3) shows diagrammatically the observed clinical effects from this therapy.

Erythema was the first sign to improve. It was also the first sign to recur when the dose of diethylstilbestrol was inadequate (Nov. 12, 1949) and when all estrogenic therapy was discontinued.

The telangiectasia lessened in size and number of vessels involved (Fig. 4), but it remained in some degree throughout the nine months of therapy.

The seborrhea did not lessen with administration of small amounts of estrogen. It seemed that not until breast hyperplasia had begun did the sebaceous gland element show dramatic response. A manifestation of this response was noted by the patient's wife in that the yellow, oily staining of the pillow (which had occurred nightly for the five years before the onset of estrogen therapy) lessened by July 1, 1949, and was absent by July 15. Even when the seborrhea returned in mild form while the amount of estrogen was inadequate (Nov. 12, 1949) and while therapy was discontinued (April 22 and Nov. 5, 1950), it was never at the pretreatment level of pillow staining. On July 1, 1949, it was noted that one cystic lesion that was filled with caseous material before the onset of therapy now contained only liquid sebum.

The size of the hyperplastic sebaceous glands never reached the normal adult level, even though clinically they were markedly reduced, and even though the secretion of sebum was within normal limits. The biopsy which was performed three months after the onset of estrogen therapy confirmed this observation. The glands were still larger than normal, and the marginal cells, as well as the cells within the center of the gland, continued to retain their nuclei. On Jan. 14, 1950, a few of the larger tumors were destroyed by electrocoagulation. There was an increase in the size of the lesions, however, when all therapy was discontinued. This was most obvious in the smaller classic, umbilicated, yellow lesions of senile sebaceous adenoma.

The onset of breast tenderness and soreness preceded the increase in the amount of breast tissue. From the clinical standpoint, we felt we could be certain that the estrogen dosage was adequate only if we were able to produce breast tissue hyperplasia in the male patient. On April 22, 1950, two months after estrogen therapy was discontinued, the breasts remained large, but the breast tissue had been replaced by fat. On Nov. 5, 1950, even this fat had disappeared, and the size and shape of the breasts had returned to their pretreatment appearance.

Libido did not begin to decrease until after two months of therapy. Sexual intercourse ceased in August, 1949, even though spontaneous morning erections continued for four more months. Within one month after the cessation of therapy, both libido and erections had returned to the pretreatment activity.

SUMMARY

A clinical evaluation of a patient with multiple tumors of senile sebaceous adenoma treated orally with diethylstilbestrol is presented. The size of the tumors was reduced, and the amount of seborrhea decreased when the diethylstilbestrol was given in adequate amounts.

CICATRIZING TINEA CAPITIS CAUSED BY TRICHOPHYTON RUBRUM (TRICHOPHYTON PURPUREUM)

MORRIS MOORE, Ph.D.
RICHARD Q. CROTTY, M.D.
AND
CLINTON W. LANE, M.D.
ST. LOUIS

TINEA capitis, or ringworm of the scalp, may be caused by various species of the genera Microsporum and Trichophyton. These lesions are characterized by loss of hair in patches with or without vesicles and pustules and with a varying degree of inflammation. Some fungi, notably Trichophyton (Achorion) schoenleini and quinckeanum, Trichophyton violaceum, and Trichophyton sabouraudi may cause atrophy of the involved scalp tissue with resultant scarring. In those patients with kerion, scarring may result from the mishandling of the lesion. Kerion may be caused by many dermatophytes.[1]

Trichophyton rubrum (Trichophyton purpureum) is the cause of characteristic clinical lesions involving the nails, glabrous skin, and the hairy regions (axillae, groin, beard, and scalp). Tinea capitis caused by Trichophyton rubrum is as yet uncommon in the United States but is more prevalent in Japan and China.[2] Three patients with tinea capitis due to this fungus have been observed in St. Louis. Two patients exhibited circinate lesions on the scalp. The one, a 12-year-old Negro boy, showed an area of inflammation and pustulation, 2 cm. in diameter, of two and one-half months' duration on the right posterior occipital region which was slightly elevated and contained many short broken-off hairs. The second patient, a 10-year-old white boy, had a circinate patch approximately 4 cm. in diameter on the right frontal region, of several months' duration, which contained grayish scales and short hairs. The third patient, presented here, had a scarring type of tinea capitis accompanied with lesions on the trunk and arms. Since this type of lesion on the scalp, caused by Trichophyton rubrum, is unusual, the case was deemed worthy of report.

REPORT OF A CASE

J. C. A., an 11-year-old white boy, was first seen on June 12, 1950, complaining of an eruption on the scalp of two years' duration. This was accompanied with an eruption on the trunk

Studies, observations, and reports from the Dermatological Department of the Barnard Free Skin and Cancer Hospital, and the Department of Medicine, Division of Dermatology, School of Medicine, Washington University, St. Louis.

1. Moore, M., and Wooldridge, W. E.: Kerion Caused by Trichophyton Sulfureum: Report of a Case, Arch. Dermat. & Syph. **6**:460-465 (March) 1950.

2. Ota, M.: Contribution to the Study of Trichophyton Purpureum Bang, Trichophyton Interdigitale Priestley and Trichophyton "B" Hodges: Also on Trichophyton "α" and Trichophyton "β" of the author, Arch. Dermat. & Syph. **5**:693-713 (June) 1922.

and arms of three years' duration. Previous treatment had consisted of application of many types of salves and liquids and no internal medication. There had been rapid progression of the condition over the scalp in the last few months (Fig. 1).

A physical examination revealed a striking eruption involving almost the entire scalp which was characterized by alopecia of the scarring type. Associated with the eruption were thick, heavy crusts which matted the hairs together at their bases. The skin of the scalp was dull red not only in the scarred areas but also under the crusts. No true scutula were seen. The ears were red and showed some papules. There was a dry scaly squamous eruption on the chest, back, and upper arms. Several of the toenails had a thickened, yellowish, hypertrophic appearance.

An ointment consisting of 5% ammoniated mercury and 5% salicylic acid in water and aquaphor® (oxycholesterol-petrolatum ointment) base was prescribed for application at night. A lotion containing 0.1% mercury bichloride and 5% resorcinol in 50% alcohol was prescribed for application twice daily. Cultures were made for fungi. Trichophyton rubrum developed in the cultures.

Fig. 1.—Cicatrizing tinea capitis caused by Trichophyton rubrum.

The patient was subsequently seen on June 23, 1950, at which time there were prescribed wet applications consisting of cupric sulfate 1.5 gm., zinc sulfate 5.6 gm. in 240 cc. of saturated camphor water, 2 tablespoons (30 cc.) to a glass of water. These wet packs were used each night and were followed by the application of zincundecate (desenex®) ointment. Zincundecate solution was applied twice daily. The patient was again seen on July 14, 1950, when the condition appeared unimproved. Aluminum acetate soaks were advised, and the condition began to subside slightly with regression of some of the crusted pustular element.

After an interval of two months, the patient was again observed, and only partial improvement was noticed. On Aug. 11, 1950, depilation with roentgen rays was performed. On Oct. 6, 1950, the patient's scalp showed almost total epilation and only a moderate number of scattered pustules. Bacitracin ointment and an antiseptic in hamamelis (witch-hazel) lotion were prescribed in an effort to control these lesions. The patient was observed over a period of several months, and the condition showed steady improvement, with a good growth of hair except in those follicles which showed the scarring alopecia at the time of the first observation. The nails still showed the mycotic involvement despite the twice-daily use of Whitfield's ointment (an ointment composed of salicylic acid, benzoic acid, and petrolatum).

The patient was last observed on May 7, 1951, at which time mycologic examination revealed active Trichophyton rubrum in the scalp and nails, although the trunk lesions had completely cleared.

MYCOLOGY

Microscopic examination of scrapings from the scalp revealed the filaments and chains of spores, arthrospores, and oidia, characteristic of a Trichophyton. On culture these cells proved to belong to Trichophyton rubrum. An examination of many hairs, on several occasions, finally showed the organism to be growing as a large-spored ectothrix (Fig. 2*A*).

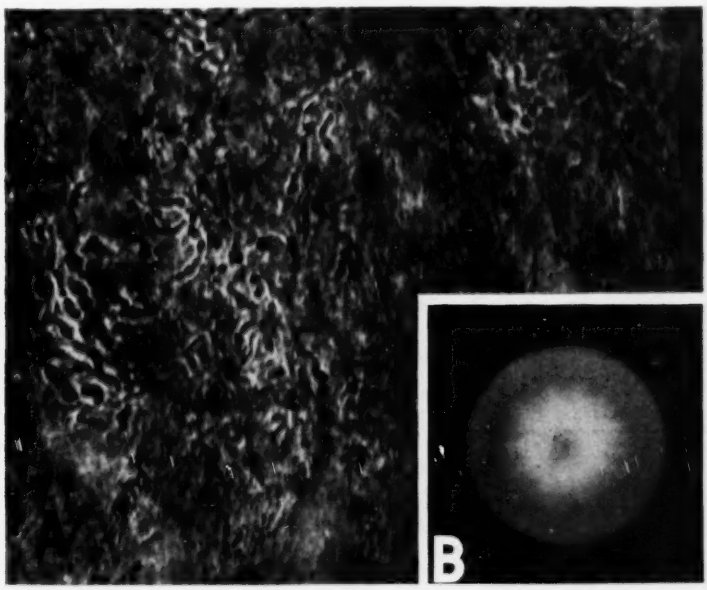

Fig. 2.—*A*, portion of hair infected with Trichophyton rubrum showing ectothrix growth. Potassium hydroxide preparation; × 650. *B*, culture of Trichophyton rubrum, 17 days old, grown on glucose-peptone agar.

The question whether this fungus is an ectothrix has been disputed. Ota [2] noted the invasion of the mycelial elements into the interior of the hair of guinea pigs infected with organisms isolated from two patients (Ichihara and Hirami), making it an endothrix. He concluded, however, that it was a Trichophyton of "endoectothrix" type. Kato, cited by Ota and Kawatsuré,[3] observed the fungus to be a large-spored endothrix in human beings, but when inoculated in animals it appeared often as an endothrix and sometimes as an endoectothrix. They concluded, therefore, that Trichophyton rubrum was an endothrix in human hair and an endoectothrix in animals. Lewis and Hopper [4] state that, "when the hair follicle is invaded the fungus

3. Ota, M., and Kawatsuré, S.: Sur le Sabouraudites ruber et ses variétés, Ann. parasitol. **11**:476-501 (Nov. 1) 1933.

4. Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, Ed. 2, Chicago, The Year Book Publishers, Inc., 1943, p. 286.

is seen to be an ectothrix Trichophyton." This observation is in agreement with our observations on the three patients seen in St. Louis. It is possible, however, that since Trichophyton rubrum does not commonly attack hair, such involvement may be simply an extension onto the hair from the involved follicle. If the organism does not have a predilection for hair, then the involvement may be only a matter of degree. Consequently one may find the ectothrix form in the early stages and the neoendothrix and endothrix forms in the advanced stages.

Grossly, Trichophyton rubrum shows several forms of colonies. This has led to several publications describing the various colonial characteristics. Muskatblit [5] has reviewed briefly many of these reports. The fungus isolated from the patient described here was grossly characteristic of that described by Bang,[6] showing a white and downy colony on glucose-peptone agar with a raised center, somewhat flattened periphery, and radial folds. The typical reddish-purple pigment of the background became noticeable through the mycelium, especially in the peripheral zone (Fig. 2*B*).

Microscopically, the colony was typical of Trichophyton rubrum with microconidia and very few macroconidia.

SUMMARY

A patient with a scarring type of tinea capitis resulting in permanent loss of hair caused by Trichophyton rubrum (Trichophyton purpureum) is presented. The fungus was found to be an ectothrix Trichophyton.

3427 Washington Ave. (3).

3720 Washington Ave. (8).

5. Muskatblit, E.: Observations on Epidermophyton Rubrum or Trichophyton Purpureum, Mycologia **25**:109-116 (March-April) 1933.

6. Bang, H.: Sur une trichophytie cutanée à grandes cercles, causée par un dermatophyte nouveau (Trichophyton purpureum Bang), Ann. dermat. et syph. **5**:225-238 (May) 1910.

CLAM DIGGER'S DERMATITIS

Schistosome Dermatitis from Sea Water

LEO ORRIS, M.D.
AND
FRANK C. COMBES, M.D.
NEW YORK

RECENTLY several cases of an eruption in clam diggers who "arm" or "toddle" hard clams in the salt water of the Long Island Sound area have come to our attention. The eruption is limited to those parts of the skin previously immersed in water.

"Arming" for hard clams is done in shallow water at low tide during the warm months, April through October. The "armer" usually lies across a rowboat, stirs up the mud with his hands, and scoops in the clams. Most "baymen" have learned by experience to wear protective clothing consisting of rubber gloves and three or four pairs of nylon stockings to cover both upper extremities from wrists to shoulders. If protective clothing is not worn, an eruption appears upon the immersed portion of their skins.

REPORT OF A TYPICAL CASE

W. D., a young man, "armed" hard clams in Cold Spring Harbor, a salt-water tributary of Long Island Sound, during the week of Aug. 20, 1951. He lay across his rowboat in the conventional manner and scooped in the clams for about three hours. Being a novice, he wore no protective clothing. Several hours later he experienced intense itching of the upper extremities, although there were no visible lesions. However, the following morning, he observed numerous discrete, red, "hive-like" papules on both forearms. These were initially about 2 mm. in diameter but gradually enlarged to about 1 cm., their summits capped by a seropurulent crust.

Although new lesions appeared daily, the patient continued to clam. By the fifth day, both upper extremities were red, swollen, painful, and covered by several dozen nodules. He applied an antihistaminic cream and hot saline compresses without relief. Fever (elevation of temperature to 101 F.), malaise, and chilliness failed to respond to antihistaminic tablets. When seen by us on the seventh day (three days after the last exposure), he was extremely uncomfortable, chilly, and feverish (temperature of 100.4 F.). Both forearms and hands were red, feverish, edematous, painful, and covered by an extensive eruption confined to those areas previously immersed in the water.

The lesions were discrete and grouped, erythematous, nodular, obtuse, pustular, and crusted, varying in diameter from 7 to 10 mm. In color and configuration they individually bore a striking resemblance to the lenticulopapular syphilid.

The patient was treated symptomatically with cold compresses, a shake lotion, penicillin given intramuscularly, and antihistaminic tablets. Within 24 hours he was much improved, and when he was last seen, seven weeks later, the eruption had disappeared except for some residual pigmentation, slight infiltration, and superficial desquamation.

The water and mud from the banks of Cold Spring Harbor were examined by Dr. Donald V. Moore, of the Department of Preventive Medicine, New York University College of Medicine, and, although snails were found in the mud, no cercariae were seen.

COMMENT

Contact dermatitis due to aquatic animals and plants may occur after immersion in fresh or salt water. In sea water, dermatitis has been reported from contact with various coelenterates (corals, hydroids, and jellyfishes), the eruption presumably due to some toxic material extruded by stinging cells (nematocysts), and from contact with spicules of the sponge (Porifera), with mollusks (terebras and poison cone shells), and with the spines of fish which sometimes have underlying poison glands.

"Swimmers' itch," customarily confined to bathers in fresh-water lakes and due to the fork-tailed schistosome cercariae, was first observed in the United States in

Clam digger's dermatitis on fifth day.

1928 among persons wading in the water of Douglas Lake in Michigan.[1] This variety of cercaria has since been reported infesting the fresh-water lakes of 12 states, Mexico, Colombia, Wales, France, Germany, Malaya and Africa. The sources of these cercariae were Trichobilharzia ocellata, Trichobilharzia stagnicolae, and Trichobilharzia physellae. An intensive study in 1945 disclosed that the natural hosts of these schistosomes are migratory birds, especially ducks.[2]

1. Cort, W. W.: Schistosome Dermatitis in the United States (Michigan), J. A. M. A. **90**:1027-1029, 1928.

2. McMullen, D. B., and Beaver, P. C.: Studies on Schistosome Dermatitis: IX. The Life Cycles of 3 Dermatitis-Producing Schistosomes from Birds and a Discussion of the Subfamily Bilharziellinae (Trematoda: Schistosomatidae), Am. J. Hyg. **43**:128-154, 1945.

The eruption in clam diggers is identical clinically to that in reported cases of schistosome dermatitis ("swimmers' itch"). Furthermore, wild ducks, sea gulls, and swans are common in the Cold Spring Harbor area, and, although reportedly fresh-water parasites, the schistosome cercariae must live facultatively in salt water, since Stunkard has reported finding them in such waters.[3]

The adult schistosomes parasitize these wild waterfowl and produce ova. Miracidia hatch from the ova, are excreted in the feces, enter snails, their intermediate host, and emerge as cercariae. In their natural hosts (waterfowl), these cercariae produce systemic infection. The snail is the only intermediate host, and if none is present the immature schistosome dies. Cercariae do not penetrate the skin while man is immersed in infested water but only later as the thin film of water remaining on the skin slowly dries. If the swimmer rubs himself dry immediately on leaving the water, he will not be infested. Cercariae accidentally ingested are destroyed immediately by the acidity of the gastric juice.

When cercariae enter the skin of man, only dermatitis results. This is a reaction to their presence in the skin. Localized itching and an urticaria-like eruption occur within a few hours. This condition is followed by the appearance of follicular papules, pustules, and edema of the exposed regions within 24 to 48 hours. The degree of reaction varies with susceptibility of the host, duration of exposure, and concentration of the cercariae. Since man is not the natural host for this type of schistosome, the cercariae are apparently destroyed in the skin, and the lesions gradually undergo involution.

"Seabathers' eruption," possibly due to the nematocysts of a coelenterate or some unicellular organism, has been reported in Florida by Sams.[4] This eruption occurred predominantly on those parts of the body covered by the bathing suit. Otherwise, it clinically resembled "swimmers' itch." We feel it is possible that these dermatoses are of identical causation. Although sea water is not the habitat of the snail vector, there is no reason why the latter cannot be washed into brackish water. The types of schistosome pathogenic to man have been found in the Orinoco, Nile, and Congo river deltas.

The predominance of the dermatitis in "seabathers' eruption" on covered parts of the body may be explained on the supposition that the hot Florida sun dries the unclothed exposed skin so quickly that the cercaria is incapable of penetrating the epidermis. The slowly drying bathing suit gives it ample opportunity to do so. Those areas not exposed to direct sunlight (axillae and inner surfaces of the arms) are involved in the dermatitis.

Histologic examination of lesions of schistosome dermatitis shows cercariae within burrows in the epidermis and a polymorphonuclear infiltrate (neutrophiles and eosinophiles) in the cutis. After about 48 hours, however, no cercariae can be demonstrated.[5]

3. Stunkard, H. W. Personal communication to the authors.

4. Sams, W. M.: Seabathers' Eruption, Arch. Dermat. & Syph. **60**:227-235, 1949.

5. Brackett, S.: Pathology of Schistosome Dermatitis, Arch. Dermat. & Syph. **42**:410-418, 1940.

In New York state, the only previous report of schistosome dermatitis was in 1947.[6] These cases were due to schistosome cercariae from infested waterfowl at Interlaken Lake, Town of Eastchester, Westchester County. In these cases cercariae were found in snails (Physa heterostropha Say) on the beach, and the schistosome, Trichobilharzia physellae, was isolated from local ducks.

SUMMARY

Clam diggers, working in the water of Cold Spring Harbor, New York, an arm of Long Island Sound, exhibit an eruption similar to schistosome dermatitis. Schistosome cercariae have been found in such waters and probably are the cause of the disease.

6. Holla, W. A., and Lane, E. A.: Report of an Itching Dermatitis Apparently Due to Schistosome Cercariae, New York J. Med. **47**:2458, 1947.

GARGOYLISM WITH CUTANEOUS MANIFESTATIONS

H. N. COLE Jr., M.D.
CLEVELAND
R. C. IRVING, M.D.
CONNEAUT, OHIO
H. Z. LUND, M.D.
R. D. MERCER, M.D.
AND
R. W. SCHNEIDER, M.D.
CLEVELAND

HURLER'S syndrome, gargoylism, lipochondrodystrophy, or dysostosis multiplex was defined by Washington as

> . . . a disease of congenital origin characterized by chondrodystrophic changes in the skeleton with a tendency toward the deposition of a lipid substance in the tissue, particularly in the brain. On pathologic examination, changes resembling those of amaurotic idiocy are found. The condition appears to combine certain features of Morquio's Disease with some features of Niemann-Pick's Disease. Clinically, it is characterized by dwarf-like stature with marked shortening of the trunk and neck; enlargement and often distortion of the skull with depression of the bridge of the nose and coarseness of facial features; limitation of motion of joints and kyphosis; protrusion of the abdomen with hepato-splenomegaly; clouding of the corneae and mental deficiency. The last two are often absent.[1]

REVIEW OF THE LITERATURE

Since as far back as 1865, a number of such syndromes have been described, characterized by physical abnormalities in specific portions of the body which tended to separate the syndromes into distinct categories.

Hunter in 1917 [2] described a condition in two brothers, 8 and 10 years of age, which was undoubtedly gargoylism. However, he did not consider it to be a specific entity.

At the suggestion of the late Meinhard Pfaundler, Hurler in 1919 [3] described the first generally accepted case of this peculiar syndrome in a 4-year-old boy. The case of a 23-month-old infant presenting a similar picture was added by Pfaundler.

From The Department of Dermatology and Syphilology, The Institute of Pathology, from the Department of Pediatrics, Western Reserve University and University Hospitals, and from the Cleveland Clinic.

1. Washington, J. A.: Lipochondrodystrophy, in Brennemann's Practice of Pediatrics, edited by J. McQuarrie, Hagerstown, Md., W. F. Prior Company, Inc., 1948, Vol. 4, Chap. 30, pp. 1-10.

2. Hunter, C.: A Rare Disease in Two Brothers, Proc. Roy. Soc. Med. **10**:104-116, 1917.

3. Hurler, G.: Über einen Typ multipler Abartungen, vorwiegend am Skelettsystem, Ztschr. Kinderh. **24**:220-234, 1919.

The possibility of this disease's belonging in the category of the lipid dystrophies was first suggested by Tuthill,[4] after he found what he interpreted to be abnormal deposits of a lipid substance in the brain of one of Hurler's patients.

The term gargoylism was introduced by Ellis, Sheldon, and Capon [5] because the large misshapen head and inhuman facies reminded them of gargoyles, i. e., grotesque figures seen on some Gothic cathedrals.

Genetics.—Because of its high familial incidence, its occurrence in infants and children, and its developmental abnormalities, the disease is universally regarded as congenital. It effects both sexes, being about 35% more frequent in the male. Also, it appears to be definitely familial in nature,[6] as it has been encountered repeatedly in two or more siblings:

An uncle of one patient reported on by Jewesbury and Spence [7] presented essentially the same features.

A maternal aunt of the patient reported on by Slot and Burgess [8] died in childhood as a deaf and dumb cripple, and a suggestive history of mental deficiency in the mother's family was given by Lachdensuu.[9]

Nja [10] studied the pedigree of a family in which five cases of gargoylism occurred. All members of the family afflicted were males to whom the trait must have been transmitted by an unaffected mother. Furthermore, in all reported cases of gargoylism that he could find in which the corneas were normal, the patients were males. Usually the disease was present in siblings or in members of the same immediate family. He, therefore, postulated that there is a sex-linked type of gargoylism.

Physical Abnormalities.—The patients are usually shorter than average, and some are pronounced dwarfs. The features are coarse and ugly. The generalized physical deformities may vary widely from one patient to another, so much so that great dissimilarities apparently exist, but, when one considers the picture of the syndrome in its entirety in comparison with an individual case, certain constant features invariably bear out the relationship.

The head is constantly large and misshapen. Scaphocephaly, brachycephaly, and oxycephaly (acrocephaly) with prominent supraorbital ridges are all described. The ears are frequently large, relatively low in position, and retracted against the head. Deafness is rarely noted. The root of the nose is often depressed, and the nares tend to be broad and tilted anteriorly. The lips are generally thick, and the tongue is often "too large for the mouth." Often there is a highly arched palate. Teeth tend to be poorly formed and widely spaced. The mandible usually presents a broad, heavy, formidable appearance. Ocular changes include interorbital distance wider than average and occasionally an internal strabismus. Highly significant,

4. Tuthill, C. R.: Juvenile Amaurotic Idiocy, Arch. Neurol. & Psychiat. **32**:198-209, 1934.

5. Ellis, R. W. B.; Sheldon, W., and Capon, N. B.: Gargoylism, Quart. J. Med. **5**:119-139, 1936.

6. Halperin, S. L., and Curtis, G. M.: The Genetics of Gargoylism, Am. J. Ment. Deficiency **46**:298-301, 1941-1942. Böcker, E.: Zur Erblichkeit der Dysostosis multiplex, Ztschr. Kinderh. **63**:688-696, 1942-1943.

7. Jewesbury, R. C., and Spence, J. C.: Two Cases (1) Oxycephaly and (2) Acrocephaly with Other Congenital Deformities, Proc. Roy. Soc. Med. **14**:30-35, 1920-1921.

8. Slot, G., and Burgess, G. L.: Gargoylism, Proc. Roy. Soc. Med. **31**:113-116, 1938.

9. Lachdensuu, S.: Vier Fälle der sogenannten Pfaundler-Hurlerschen Krankheit, Monatsschr. Kinderh. **92**:340-355, 1943.

10. Nja, A.: A Sex-Linked Type of Gargoylism, Acta pædiat. **33**:267-286, 1945-1946.

but by no means a constant feature, is a diffuse or spotty cloudiness of the cornea interfering with vision.[11]

The neck is short and, together with the massive skull, gives the impression that the head is resting directly on the torso. The thorax is large and appears emphysematous in type. A pronounced dorsolumbar kyphosis is described as a more or less classic characteristic of the syndrome.[12]

The abdomen is scaphoid and protuberant; sometimes, although not invariably, these characteristics are the result of an enlargement of the liver and spleen.[13] Umbilical and inguinal hernias are frequently present.

With but one exception,[5] the most constantly appearing abnormality is the flexion deformity of the extremities. This is characterized by a pronounced limitation of extension but with no interference in flexion of the involved joints and is most frequent in the fingers. Larger joints, elbows, shoulders, hips, and knees are often involved. Coxa valga, genu valgum, talipes equinovarus, pes planus, and pes cavus also are not infrequent. The extremities have been described as being stumpy and appearing shorter than usual.

Pathology.—Roentgenologic Findings: Roentgenographic examination of the skull sometimes reveals widening of the suture lines, a large anterior fontanel, and occasional bony ridges. The finding of an enlarged sella turcica is not a particularly frequent one.[14]

The vertebral bodies tend to be somewhat narrow, especially in the cervical region. The ribs are usually fixed in a horizontal position, and the distal portions show varying degrees of broadening. The clavicles are often massive and heavy. The scapulae are frequently revealed in an elevated position. Long bones and phalanges are not infrequently described as somewhat shorter and broader than usual, with delayed centers of ossification in some.

These bone changes are by no means constant, since patients with no significant bony abnormality or roentgen changes have been described.[15]

Bone Changes: Washington[1] found that microscopic sections of the epiphyses showed evidence of slowness and irregularity of cartilage growth, which he thought to be the seat of the disturbance in skeletal development. He felt that the kyphosis is presumably due to the effect of mechanical stress upon the vertebral bodies, the

11. (*a*) Harvey, R. M.: Hurler-Pfaundler Syndrome, Am. J. Roentgenol. **48**:732-740, 1942. (*b*) Hubeny, M. J., and Delano, R. J.: Dysostosis Multiplex, ibid. **46**:336-342, 1941. (*c*) Lurie, L. A., and Levy, S.: Gargoylism, Am. J. M. Sc. **207**:184-185, 1944. (*d*) Rose, J. R.; Hawke, W. A., and Brown, A.: Gargoylism, Arch. Dis. Childhood **16**:71-80, 1941.

12. (*a*) Jewesbury and Spence.[7] (*b*) Slot and Burgess.[8] (*c*) Footnote 11 *a*, *c*, and *d*. (*d*) Engel, D.: Dysostosis Multiplex, Arch. Dis. Childhood **14**:217-230, 1939. (*e*) Helmholz, H. F., and Harrington, E. R.: A Syndrome Characterized by Congenital Clouding of the Cornea and by Other Anomalies, Am. J. Dis. Child. **41**:793-800, 1931. (*f*) ten Bokkel Huinink, A.: Gargoylism, Maandschr. kindergeneesk. **6**:449-451, 1937. (*g*) Veasey, C. A.: Ocular Findings Associated with Dysostosis Multiplex and Morquio's Disease, Arch. Ophth. **25**:557-563, 1941.

13. (*a*) Jewesbury and Spence.[7] (*b*) Helmholz and Harrington.[12e] (*c*) Binswanger. E., and Ullrich, O.: Über die "Dysostosis multiplex" (Typus Hurler) und ihre Beziehungen zu anderen Konstitutionsanomalien, Ztschr. Kinderh. **54**:699-712, 1933.

14. (*a*) ten Bokkel Huinink.[12f] (*b*) Kressler, R. J., and Aegerter, E. E.: Hurler's Syndrome, J. Pediat. **12**:579-591, 1938. (*c*) Liebenaur, L.: Beitrag zu Dysostosis multiplex, Ztschr. Kinderh. **59**:91-123, 1937. (*d*) Ruggles, H. E.: Dwarfism Due to Disordered Epiphyseal Development, Am. J. Roentgenol. **25**:91-99, 1931.

15. Hunter.[2] Footnote 12 *d* and *e*.

cartilages of which lack the capacity for normal growth, and explained the shortening of the thorax and neck as a result of the failure of the vertebral bodies to grow to full height. The restriction of motion of the joints of the extremities is, in his opinion, due to the improper formation of the articular surfaces.

The abnormalities of the skull cannot be readily explained. Depression of the bridge of the nose may occur as a result of improper growth of the basilar bones, which are derived from cartilage, but scaphocephaly and premature closure of the sagittal suture by the union of the two parietal bones, so often present, cannot be attributed to chondrodystrophy. This may result from a defect in the blastemal capsule and mesodermal *Anlage* of the top of the skull.[16]

L. Strauss [17] felt that the disturbance of the function of the perichondrium and periosteum leads to the skeletal deformities, on the basis of vacuolated cells found in the periosteum.

Schmidt's observation [18] of what he considered to be lipid storage in cartilage cells in epiphyses could not be confirmed by Kny [19] or by L. Strauss.[17]

Kressler and Aegerter [14b] reported that microscopic examination of bone revealed "normal ossification and healthy bone growth."

Central Nervous System: The presence of an abnormal deposition of a lipid substance was first pointed out by Tuthill [4] in his report of the histologic examination of the brain of one of Hurler's patients.

In all autopsied cases available for study in which examination of the brain was carried out, microscopic sections showed many of the ganglion cells to be filled with granular deposits of a foreign substance. In these cells, the nuclei were pushed to one side and the Nissl substance showed degeneration or was absent. The neurofibrils were at times stretched about the periphery of the cell. Among the brains examined, there was considerable variation in the number of cells affected.[20]

The finding of almost identical nerve-cell changes in a variety of conditions (Gaucher's disease, Niemann-Pick disease, amaurotic idiocy, gargoylism) raises the question of the extent to which these central nervous system changes are specific. Globus expressed the view that swelling of nerve cells and the appearance in them of a fat-like substance probably indicate a local disturbance of cellular metabolism.[21]

16. Park, E. A., and Powers, G. F.: Acrocephaly and Scaphocephaly with Symmetrically Distributed Malformations of the Extremities, Am. J. Dis. Child. **20**:235-315, 1920.

17. Strauss, L.: Pathology of Gargoylism, Am. J. Path. **24**:855-888, 1948.

18. Schmidt, M. B.: Die anatomischen Veränderungen des Skeletts bei der Hurlerschen Krankheit, Zentralbl. allg. Path. **79**:113-123, 1942.

19. Kny, W.: Zur Kenntnis der Dysostosis multiplex Typ Pfaundler-Hurler, Ztschr. Kinderh. **63**:366-377, 1942-1943.

20. (*a*) Tuthill.[4] (*b*) Kressler and Aegerter.[14b] (*c*) Strauss.[17] (*d*) Kny.[19] (*e*) Reilly, W.: An Atypical Familial Endocrinopathy in Males with a Syndrome of Other Defects, Endocrinology **19**:639-648, 1935. (*f*) Ashby, W. R.; Stewart, R. M., and Watkin, J. H.: Chondro-Osteo-Dystrophy of the Hurler Type: A Pathological Study, Brain **60**:149-179, 1937. (*g*) Green, M.: Gargoylism, J. Neuropath. & Exper. Neurol., to be published. (*h*) de Lange, C.: Dysostosis Multiplex, Psychiat. en neurol. bl. **46**:2-18, 1942.

21. Globus, J. R.: Amaurotic Family Idiocy, J. Mt. Sinai Hosp. **9**:451-503, 1942-1943.

The majority of reported patients are mentally defective in a variable degree. Many, however, have normal intelligence, and an occasional patient exhibits intelligence greater than normal.[22]

Approximately one-quarter of the reported patients show no central nervous system and ocular involvement.[1]

Ocular Changes: An increase in the interorbital distance and internal strabismus have occasionally been reported, but by far the most significant ocular change is a diffuse or spotty cloudiness of the cornea which may interfere with vision. It has been known to appear as early as 6 months of age and has been attributed to either a corneal dystrophy [23] or a lipid infiltration.[24]

Defects in Bowman's membrane which contained vacuolated cells with granules in their cytoplasm have been described by Berliner,[25] Rochat,[26] and von Zeeman.[27] Berliner considered them lipid granules. Rochat mentioned that the granules were soluble in ether and alcohol, were not doubly refractile, and gave a pale yellow-brown stain with Sudan III.

Endocrine Changes: No constant abnormalities of the glands of internal secretion are found. An enlargement of the sella turcica is reported in about one-half of the cases, but this may occur without actual enlargement of the pituitary gland. In the thyroid gland the picture varies from that of hypoplasia to that of mild hyperplasia. In two cases in which creatine excretion studies were done, no variation from normal was observed. Hypogenitalism is generally present in females who have passed the age of puberty, whereas, males as a rule, show well-developed sex organs.

Kressler and Aegerter [14b] described the pituitary gland as enlarged and showing an infiltration of chromophobe cells.

In de Lange's case [20h] the pituitary gland showed degenerative changes and loss of chromophobe cells.

The first of two patients reported on by Ashby and associates presented a thyroid gland of the "foetal type" microscopically, and in the other patient the thyroid gland showed "moderate interstitial fibrosis." The pituitary gland of the former patient was describd as "slightly hyperplastic."[20f]

In Reilly's case, the thyroid gland showed "slight interstitial fibrosis and hyperplasia." Focal necrosis of the anterior lobe of the pituitary gland was also observed.[20e]

Thyroid, pituitary, thymus, adrenal glands, and ovaries were all described as normal in L. Strauss' case.[17]

Visceral Changes: Kressler and Aegerter [14b] were the first to stress widespread visceral changes characterized by the presence of vacuolated cells in many organs, particularly the liver, spleen, lymph nodes, and myocardium. In their case, the liver and spleen were moderately enlarged. Histologically, the liver presented considerable vacuolation of the parenchymatous cells, which resembled a severe fat phanerosis. A small number of vacuolated cells was seen in the spleen. Large

22. (*a*) Footnote 11 *a* and *b*. (*b*) Footnote 12 *d* and *e*. (*c*) Lieberman.[14c] (*d*) Ashby and others.[20f] (*e*) Meyer, S. J., and Okner, H. B.: Dysostosis Multiplex with Special Reference to Ocular Findings, Am. J. Ophth. **22**:713-722, 1939.

23. Ellis and others.[5] Ellis, R. W. B.: Gargoylism, Proc. Roy. Soc. Med. **31**:710-726, 1938.

24. Helmholz and Harrington.[12e] Kressler and Aegerter.[14b] Meyer and Okner.[22e]

25. Berliner, M. L.: The Keratitis of Hurler's Syndrome, to be published.

26. Rochat, G. F.: Die Corneaveränderungen bei der Dysostosis multiplex, Ophthalmologica **103**:353-356, 1942.

27. von Zeeman, W. P. C.: Gargoylismus, Acta ophth. **20**:40-47, 1942.

vacuolated endothelial cells were described in the lungs. Many of the lymph nodes were enlarged, and prominent nests of vacuolated cells replaced large areas of the pulp. In places, the myocardial fibers were similarly involved. In the hematoxylin-eosin-stained sections, the alteration of the tissues resembled a lipid infiltration, but the areas failed to stain with the usual fat stains. No anisotropic bodies were seen with polarized light. Because of the failure to demonstrate the presence of a lipid by the usual methods, the infiltrating substance was believed to be a "conjugated lipoid."

Similar attempts to demonstrate the presence of a lipid by L. Strauss,[17] R. Strauss, Merliss, and Reiser,[28] and others have likewise been unsuccessful.

The liver in L. Strauss' case [17] showed involvement of Kupffer cells, in addition to extensive vacuolation of parenchymal cells.

Kny [19] found no microscopic changes in the spleen, while the liver was described as showing early cirrhosis and vacuolation of the liver cells. The Kupffer cells, however, appeared free of changes.

In Reilly's case,[20e] microscopic examination showed nothing more than slight increase in interlobular connective tissue.

Splenectomy and biopsy of the liver in a 2-year-old boy reported on by Ellis [29] revealed an enlarged spleen with hyperplasia of the pulp. Liver cells were described as "well filled with glycogen." Search for abnormal lipids gave negative results.

A biopsy specimen of the liver from the first patient of Debré, Marie, and Thieffry [30] showed no histologic or histochemical abnormality.

Thus, involvement of the reticuloendothelial system is not a prominent or constant feature of gargoylism. The extensive involvement of mesenchymal structures, endocardium, myocardial connective tissue, and intima and media of large and medium-sized arteries, with an increase of collagen fibers, has apparently not been frequently observed, although several gross reports have described chronic endocarditis with fibrous thickening of the valves and yellowish intimal plaques in the aorta.[31]

Chemical Studies: The first chemical analysis for lipids in different organs was carried out by Holden and Thannhauser.[32] With the exception of the spleen, in which a slight increase in cerebrosides was found, all lipid fractions including neutral fat, cholesterols, lecithin, and cephalin, as well as sphingomyelin, were demonstrated to be present in normal amounts. Thus, they felt it improbable that the syndrome is related directly to any of the known diseases in which an accumulation of one or the other of these lipids within the cell is pathognomonic of the disease. However,

28. Strauss, R.; Merliss, R., and Reiser, R.: Gargoylism, Am. J. Clin. Path. **17**:671-694, 1947.

29. Ellis, R. W. B.: Gargoylism, in British Encyclopedia of Medical Practice, edited by R. Rolleston, London, Butterworth & Company, Ltd., 1937, Vol. 5, pp. 496-501.

30. Debré, R.; Marie, J., and Thieffry, S.: La polydystrophie de Hurler: Le "gargoylisme" d'Ellis (à l'occasion de trois observations nouvelles), Semaine hôp. Paris **22**:309-320, 1946.

31. Nja,[19] Reilly,[20e] Stoeckel, K. H.: Über zwei Fälle von Chondro-Osteo-Dystrophia von Typus Hurler, Monatsschr. Kinderh. **86**:348-368, 1941. Wolff, D.: Microscopic Study of Temporal Bones in Dysostosis Multiplex, Laryngoscope **52**:218-223, 1942.

32. Thannhauser, S.: Lipoidoses: Diseases of the Cellular Lipid Metabolism, New York, Oxford University Press, 1950.

these authors recognized the possibility of there being a lipid so firmly bound to protein (lipoprotein) that an extraction with the usual fat solvents would be impossible.

R. Strauss, Merliss, and Reiser [28] likewise found no marked change in any lipid constituent in brain, liver, and spleen. However, they found the lipid composition of lymph nodes to differ significantly from the normal by a decrease in total phospholipids and by an increase in "rest lipids." They also found a relatively great percentage increase in cerebrosides.

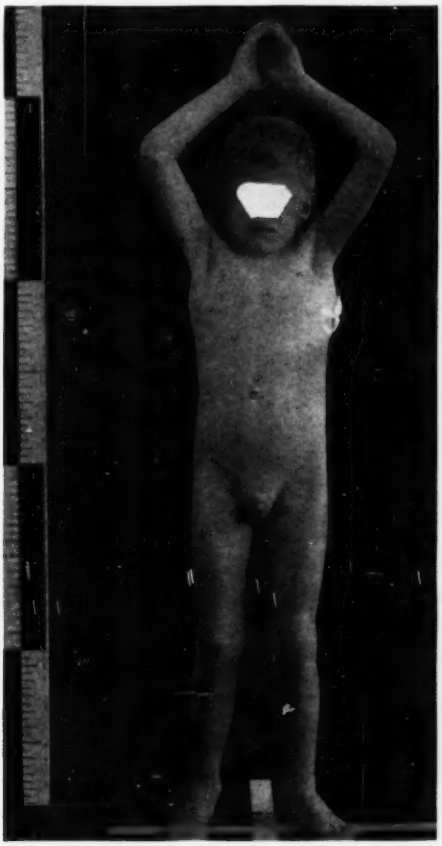

Fig. 1 (Case 1).—Flexion deformity of fingers, limitation of extension of elbows, and limitation of abduction of arms above head.

CASE HISTORIES

CASE 1.—R. M., a 6-year-old white boy of Hungarian and English extraction, was admitted to the Pediatric Service of the University Hospitals on July 27, 1950. There was no history of consanguinity in the parents. The patient had a 2-year-old sister who was perfectly normal. There were no other pregnancies. Further pertinent family history revealed that the mother had two brothers and two sisters (one of the brothers is reported on as our Case 2). The other brother died at the age of 28 years as the result of complications following a hernia repair

operation. He, too, apparently, had many of the physical deformities associated with gargoylism except for the fact that he was of normal stature and not a dwarf. One sister had a small boy who showed these same abnormalities, including a massive skull, flexion deformity of the hands, difficulty in hearing, and an inguinal hernia. The other sister had an 8-year-old boy who was apparently normal.

The patient's development in infancy was not unusual, except for the fact that he was unable to raise his arms straight above his head or to straighten his fingers completely. Also,

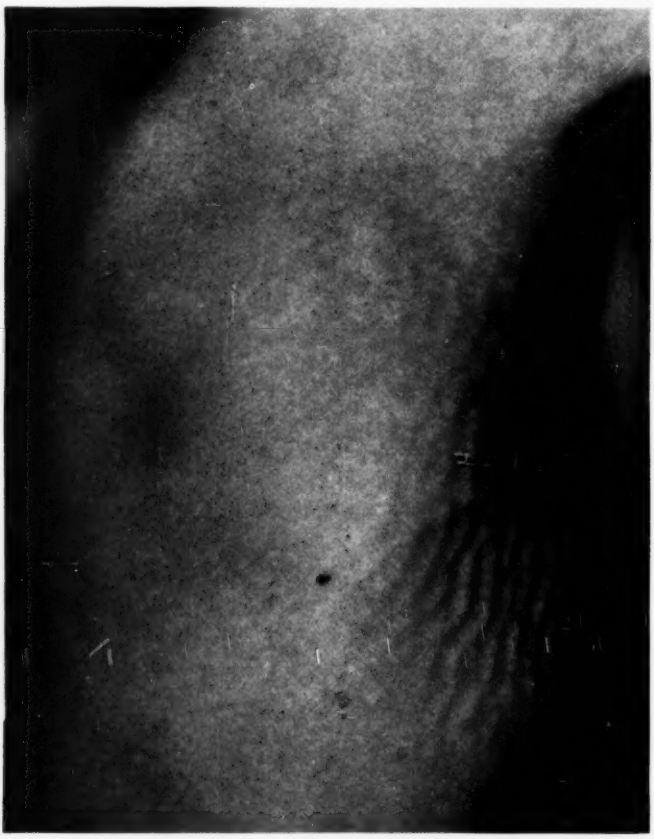

Fig. 2 (Case 1).—Furrowing of skin over lateral thorax.

enlargement of the spleen was noted from birth. At the age of one year the peculiar furrowing of the skin over the upper arms and thoracic cage was noted. Since 2 years of age, the somewhat massive appearance of the skull, the coarseness of facial features, and an impairment in hearing have gradually become more pronounced.

Results of Physical Examination.—The head of the patient appeared relatively large. The frontal bones and supraorbital ridges were prominent, while the bridge of the nose appeared depressed. The hair was coarse and brittle. The eyes were rather widely spaced. The corneas were clear; vision was normal, and the fundi showed normal disks. There was definite diminution of hearing bilaterally. The lips were thick and the teeth rather poorly spaced. The skin in the posterior axillary line, over the shoulders and lateral thorax bilaterally, showed pronounced

furrowing, with the ridges 0.5 to 0.75 cm. in height, the distance between them being the same. The ridges were smooth and rather firm and looked like old ivory. The neck did not appear abnormally short. The chest was clear to auscultation and percussion. Examination of the heart revealed a soft systolic apical murmur, but findings otherwise were normal. The abdomen was scaphoid. The liver edge was palpable at the level of the umbilicus. It was firm and nontender. The edge of the spleen extended to the iliac crest and was firm and slightly tender. The back showed no evidence of kyphosis. The external genitalia appeared normally developed,

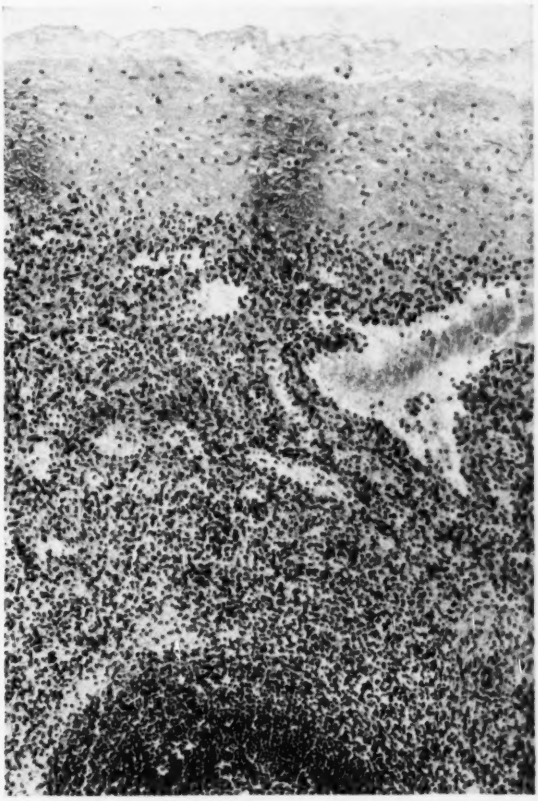

Fig. 3 (Case 1).—Spleen. Slight thickening of capsule and follicular hyperplasia. × 94.

and the testes were descended. Examination of the joints revealed that the fingers were flexed and could not be fully extended. There was limitation of extension of the elbows, and the arms could not be abducted above the head.

Laboratory Findings.—The hemoglobin concentration was 85%; the white blood cell count was 5,050, with 24 polymorphonuclear leucocytes, 69 lymphocytes, 3 monocytes, 1 plasma cell, and 3 unidentified cells per 100 cells. The urogram showed no abnormalities. A serologic test of the blood was negative. Serum phosphorus was 5.6 mg.; serum calcium, 9.9 mg; blood cholesterol, 161 mg.; cholesterol esters, 131 mg., and total blood lipids, 645 mg., per 100 cc. The basal metabolic rate was + 8%. Examination of contents of a sternal marrow aspiration showed a normal picture.

Roentgenologic examination of the skull, chest, and entire bony structure revealed no abnormalities, and bone age was reported as normal.

Splenectomy was performed on the seventh hospital day. The spleen weighed 290 mg. and measured 15 by 9 by 4.5 cm. On gross examination the serosal surface was in some parts purple and in other areas red. The surface appeared to be finely pitted and was covered by a smooth membrane. On section, numerous white follicles were observed which measured 0.1 cm. in diameter. The cut surface seemed slightly firmer than normal. Microscopic examination showed a moderate degree of follicular hyperplasia. No vacuolated cells were observed. Sudan stains for lipid revealed none.

Histologic examination of a skin biopsy specimen disclosed the following: The epidermis showed normal thickness and cellular detail. The cutis was increased in thickness. Collagen fibers were arranged irregularly and appeared to be broken in numerous foci. They were widely separated by lipid-like tissue which appeared edematous. Fat stains on this tissue showed no

Fig. 4 (Case 1).—Skin. Marked fragmentation of collagen fibers and mucinous degeneration. × 200.

abnormal amounts of fat. Mucin stains disclosed that the lipid tissue was strongly positive for mucin. It was distributed diffusely throughout the cutis but was denser adjacent to foci of fat and skin appendages.

Case 2.—C. G., a 23-year-old white man of Hungarian extraction and uncle of the first patient, was studied at the Cleveland Clinic in 1945 by one of us (R. W. S.). The earliest evidence of any abnormality, noted sometime in the first year, was his inability to raise his arms above his head and to extend the fingers completely. He stated that the curious furrowing of the skin over the shoulders and thorax similar to that seen in Case 1, developed in the first year or two but that this condition disappeared at the age of 12 years. Occasional petit mal and grand mal seizures made their appearance at the age of 16 years. Partial loss of hearing was also noted early in life and was a handicap in school, but, in spite of this, the patient was graduated from high school at the age of 19 years. In 1947 an inguinal hernia developed, which was repaired.

Results of Physical Examination.—The patient was a well-developed, alert, affable dwarf, who measured 59 in. (150 cm.) in height. He had the appearance of a dyschondroplastic dwarf with acromegaly. The skull was scaphocephalic, being shaped like the breastbone of a bird. The frontal and occipital prominences were marked, as were the supraorbital ridges. There was a massive, heavy-set jaw. The hair was very coarse in texture, as was the skin on the face. The eyes were widely spaced. The corneas were clear. The nasal bridge was flat and broad. The lips were thick and the teeth poorly spaced. The neck seemed very short, and this, together

with the fact that the trapezii were set high, gave an appearance of the head resting directly on the shoulders. Examination of the chest and cardiovascular system revealed no abnormalities. The abdomen was flat, and there were no masses palpable. The external genitalia were well developed. Examination of the skeletal system revealed that the patient was unable to extend the fingers and elbows completely or to abduct the arms above the head. The hands appeared short and the fingers broad. There was no kyphosis.

Laboratory Findings.—Red blood cells numbered 5,180,000; the white blood cell count was 2,950, with 40% polymorphonuclear leucocytes and 60% lymphocytes. Urinalysis revealed no abnormalities. A serologic test of the blood was negative. Blood sugar (fasting) was 104 mg. and blood cholesterol 126 mg. per 100 cc. The basal metabolic rate was + 3%.

Fig. 5 (Case 2).—Dwarf-like stature, massive skull, and coarse facial features.

Roentgenograms of the skull showed the following: The sutures were fused, and the lines were obliterated. The frontal bone overhung the orbits. The nasal bones were short. The incisor teeth protruded, and the angles of the mandible were more obtuse than usual. The anterior cranial fossa was shortened, and the sella turcica was not enlarged or eroded. Bone age was normal.

COMMENT

Standard pediatric texts classify gargoylism as lipo-osteochondrodystrophy which is congenital and familial in nature. The pronounced physical abnormalities that are invariably present to a greater or less degree make it apparent that there is some fundamental disturbance in the growth of bone and cartilage, but the mechanism responsible for this remains obscure. That the condition is a lipid-

storage disease related to Niemann-Pick disease and other similar entities is as yet unproved. This premise is based upon the rather inconsistent finding of vacuolated cells in various organs and tissues. Actually, however, it has never been satisfactorily demonstrated that such cells contain a lipid material. In this connection it should be pointed out that histochemical demonstration of lipids in tissue is often obscured by their conjugation with proteins and carbohydrates. Quantitative analysis of tissues in the case reported by Merliss, Reiser, and Strauss [28] revealed a significant increase in lipid content of lymph nodes, but not of the brain, liver, or spleen. They concluded that by exclusion the increased lipid was simple fat probably in complex protein combination, and the fact that it was not a phospholipid, cerebroside, or cholesterol should distinguish this disturbance from other idiopathic lipid dystrophies.

The high familial incidence (48%) among twins and siblings favors a congenital factor as a cause. It is apparent that more than one genetic pattern plays a role in its production. In Nja's cases,[10] as well as in ours, the condition was sex-linked, occurring only in males and transmitted by females, whereas it is well recognized that the disturbance does occur in females, although about 35% less frequently. It would seem that the genetic mechanism involved in a given case is probably a determining factor of the degree of severity. Nja [10] pointed out that in all reported cases he could find of gargoylism with normal corneas the patients were males. It is suggested that the severer manifestations, such as corneal opacities and mental deficiency, may be less frequent in the sex-linked type of gargoylism occurring in males than in the types in which other genetic formulas are responsible.

The disease cannot be attributed to an endocrine disorder. Metabolic studies have given normal results. In addition, no known glandular dysfunction produces lesions such as are present, nor have autopsies revealed any constant abnormalities of the glands of internal secretion.

To account for the syndrome as simply a familial bone disease belonging to the group of hereditary osteochondrodystrophies offers no explanation for such features as enlargement of liver and spleen, cloudiness of the corneas, and involvement of the skin as in one of our patients.

The hypothesis offered by Engel,[12d] which assumes mechanical interference with normal growth of primordial structures, including the pituitary hypothalamic mechanism that controls lipid metabolism, on the basis of the escape of blebs of cerebrospinal fluid in embryonic life, is not borne out by any anatomic evidence of this interference at birth.

The suggestion of R. Strauss, Merliss, and Reiser [28] that the primary disorder is in the collagen, chiefly of fascia and ligaments, seems worthy of due consideration. Their basic premise for this theory lies in the similarity of the "claw-like" flexion deformity of the hands in gargoylism to Dupuytren's contracture. They point out that normal bony growth could be interfered with by circumscription of and production of unequal tensions on bones by abnormally rigid fascia and tendinous structures. They also suggest that since bone and cartilage are mesodermal derivatives it is possible that they could be directly influenced in the process of formation by the factors that influence the development of fascia. In support of this view, these authors point out the presence of unusually thick fascia of the abdominal wall and that overlying the spine as observed in their case. They also refer to the furrow-

ing of the scalp, which would presumably be due to contracture of the galea aponeurotica, in support of a collagen disorder.

The occurrence of inguinal hernias in early childhood, as observed in our cases and frequently mentioned elsewhere in the literature, might be explained on such a basis, as well as the prominent furrowing of the skin over the upper arms and thorax of one of our patients.

SUMMARY AND CONCLUSIONS

Two cases of gargoylism are presented, together with a review of the literature.

It is shown that in this particular instance a sex-linked type of inheritance applied. The condition was transmitted by female members of the family and affected only their male offspring. Obviously, this mechanism could not explain those cases reported in females or many of those reported in males in which no such relationship could be shown to exist, but it is very suggestive that the abnormalities are probably initiated by congenital factors.

Evidence is submitted in support of the theory that this condition is basically a disease of collagen connective tissue rather than a form of lipochondrodystrophy.

If the disease is related to the group of idiopathic lipid dystrophies, the lipid must be in the form of a conjugated lipoprotein which cannot be readily extracted by the usual fat solvents or stained by the usual methods.

ULCERS OF THE LEG IN FELTY'S SYNDROME

EUGENE P. SCHOCH Jr., M.D.
MINNEAPOLIS

FIVE CASES of chronic rheumatoid arthritis, splenomegaly, and leucopenia in middle-aged adults were described by Felty [1] in 1924. Other somewhat inconsistent clinical features included slight secondary anemia, lymphadenopathy, low-grade fever, weight loss, and yellowish-brown pigmentation and dusty nodules in the skin. Still [2] previously had described a form of chronic arthritis occurring in children, accompanied with lymphadenopathy and splenomegaly, but with leucocytosis rather than leucopenia. Chauffard and Raymond [3] similarly had reported adenopathy occurring in adults with rheumatoid arthritis. Thus, the somewhat confused literature has referred to a heterogeneous group of conditions as Still-Chauffard-Felty's disease.

There have been numerous reports of cases fitting Felty's original description.[4] A statistical review of cases of rheumatoid arthritis supports Felty's original concept that the syndrome is a single pathologic process caused by a noxa which affects the joints, spleen, and leucocytes. However, such a review questions the probability that this symptom complex is an entity. One to 20% of patients with rheumatoid arthritis have splenomegaly,[5] and 6 to 22% have leucopenia.[6] Comroe and Michael [7]

From the Division of Dermatology, University of Minnesota, H. E. Michelson, M.D., Director, and the Department of Dermatology, Minneapolis General Hospital, Carl W. Laymon, M.D., Director.

1. Felty, A. R.: Chronic Arthritis in the Adult Associated with Splenomegaly and Leukopenia, Bull. Johns Hopkins Hosp. **35**:16, 1924.

2. Still, G. F.: On a Form of Chronic Joint Disease in Children, Tr. Med. Chir. Soc. Edinburgh **80**:47, 1896-1897.

3. Chauffard, A., and Raymond, F.: Des adenopathies dans le rhumatisme chronique infectieux, Rev. méd. **16**:345, 1896.

4. (*a*) Price, A. E., and Schoenfeld, J. B.: Felty's Syndrome, Ann. Int. Med. **7**:1230, 1934. (*b*) Reich, C.: A Case of Felty's Syndrome, M. Rec. **144**:488, 1936. (*c*) Williams, R. H.: Felty's Syndrome, Report of a Case with Necropsy Findings, Ann. Int. Med. **9**:1247, 1936. (*d*) Lockie, L. M.; Sanes, S., and Vaughan, S. L.: Chronic Arthritis Associated with Neutrophilic Leukopenia, Splenomegaly and Hepatomegaly, Am. J. Clin. Path. **17**:26, 1942. (*e*) Hirschboeck, J. S.: Hematologic Effects of Splenectomy in Still-Chauffard-Felty's Syndrome: A Report of 2 Cases, Blood **1**:247, 1946.

5. (*a*) Hench, P. S., in discussion on Singer, H. A.: Etiology of Felty's and Related Syndromes, J. A. M. A. **101**:2078, 1933. (*b*) McCrae, T.: Arthritis Deformans: The Report of 110 Cases from the Johns Hopkins Hospital, ibid. **42**:1, 1904. (*c*) Dawson, M. H.: Chronic Arthritis, in Nelson New Loose-Leaf Medicine, New York, Thos. Nelson & Sons, 1935, pp. 605-644. (*d*) Comroe, B. I.: Arthritis and Allied Conditions, Philadelphia, Lea & Febiger, 1940.

6. McCrae,[5b] Eaton, E. R.: Chronic Arthritis: A Report Based on the Study of the Blood Cell Count in Two Hundred Fifty Cases, J. Am. Inst. Homeop. **25**:125, 1932.

7. (*a*) Comroe,[5d] (*b*) Michael, M.: Disorders of the Joints, in Principles of Internal Medicine, edited by T. R. Harrison, Philadelphia, The Blakiston Company, 1950, p. 474.

favored Felty's second explanation, that is, that the syndrome is merely a combination of two separate clinical entities occurring coincidentally in the same person. They considered that the syndrome is merely a variant of rheumatoid arthritis and that there are other causes for the splenomegaly and leucopenia.

PATHOLOGY

In rheumatoid arthritis Hench [8] showed pathologic changes in tissues other than the joints which indicated that the disease is a generalized process. On this basis, involvement of the skin, muscles, spleen, liver, lymph nodes, and marrow could be expected. At the University of Michigan Curtis and Pollard [9] studied three variants of rheumatoid arthritis: (1) complete Felty's syndrome, (2) arthritis, splenomegaly, and leucocytosis, and (3) arthritis without splenomeglay or leucopenia. Changes in the bone marrow, lymph nodes, and spleen were those resulting from chronic infection. Biopsy specimens were taken from the skin of the calf and the underlying muscle. Histologic examination of the skin showed atrophy of the epidermis and fibrosis of the corium. Sections of the underlying muscle presented an increase of the interstitial nuclei and small perivascular infiltrates throughout the entire muscle. The character of the infiltrate is thought by some to be diagnostic of rheumatoid arthritis.[10] On a pathologic basis it was concluded that the combination of arthritis, splenomegaly, and leucopenia is due to chance and does not constitute a specific syndrome.

TREATMENT

Because the leucopenia in Felty's syndrome has been considered to be due to an increased destruction of leucocytes in the spleen and/or splenic "toxic" depression of the marrow, splenectomy has been advocated. Hanrahan [11] in 1932 and Craven [12] in 1934 were the first to perform the operation in two such cases. There was immediate temporary improvement, although the patients died 14 and 18 months after the operation. Regardless of these outcomes, the procedure remains popular. Of 15 patients so treated up to 1950, at least 10 had temporary improvement of the leucopenia, and 7 had remissions of the arthritis.[13]

Ulcers of the leg were not described in Felty's original report, nor have others included them as a consistent part of the symptom complex. Such an occurrence

8. (*a*) Hench.[5a] (*b*) Hench, P. S.; Bauer, W.; Fletcher, A. A.; Ghrist, D.; Hall, F., and White, T.: The Problem of Rheumatism and Arthritis: Review of American and English Literature for 1935, Ann. Int. Med. **10**:754, 1936.

9. Curtis, A. C., and Pollard, H. M.: Felty's Syndrome: Comparison of Felty's Syndrome with Other Forms of Rheumatoid Arthritis, Ann. Int. Med. **13**:2265, 1940.

10. Steiner, G., and Chason, J. L.: Differential Diagnosis of Rheumatoid Arthritis by Biopsy of Muscle, Am. J. Clin. Path. **18**:931, 1948.

11. Hanrahan, E. M., and Miller, S. R.: Effect of Splenectomy in Felty's Syndrome, J. A. M. A. **99**:1247, 1932.

12. Craven, E. B.: Splenectomy in Chronic Arthritis Associated with Splenomegaly and Leukopenia (Felty's Syndrome), J. A. M. A. **102**:823, 1934.

13. Rogers, H. M., and Langley, F. H.: Neutropenia Associated with Splenomegaly and Atrophic Arthritis (Felty's Syndrome): Report of a Case in Which Splenectomy Was Performed, Ann. Int. Med. **32**:745, 1951.

has been reported, however, in three cases.[14] The rarity of ulcers of the leg in Felty's syndrome and the possibility that dermatologists are not generally aware of this obscure cause of ulcers are the reasons for reporting two additional cases.

REPORT OF CASES

CASE 1.—E. S., a white man aged 51 years, had moderately severe rheumatoid arthritis for 29 years. During his first hospitalization at the Minneapolis General Hospital, in 1947, he had an associated splenomegaly and leucopenia. On subsequent admissions to the hospital in 1949 and 1950, the consistent presence of the same triad led to a diagnosis of Felty's syndrome. A transient, purpuric eruption was present during the first three days of the last hospitalization.

On April 24, 1950, the patient was admitted to the dermatology service because of an ulcer of two weeks' duration on the left medial malleolus. The circular lesion measured 2 cm. in diameter and was covered by a tenacious, gray, necrotic membrane. The rest of the physical examination revealed nothing remarkable except for chronic arthritic deformities of the meta-

Fig. 1 (Case 1).—Histologic section of lesion showing nonspecific ulceration. Hematoxylin-eosin stain; × 50.

carpal-phalangeal, metatarsal-phalangeal, elbow, and knee joints and an enlarged, painless spleen palpable 6 cm. below the left costal margin.

Laboratory studies of the blood showed hemoglobin content ranging from 12 to 14.2 gm. per 100 cc.; red blood cell counts, from 3,900,000 to 4,700,000; thrombocytes, from 100,000 to 240,000, and leucocytes, from 950 to 3,300 per cubic millimeter; polymorphonuclear neutrophiles ranged from 18 to 50%; lymphocytes, from 45 to 66%; monocytes, from 2 to 7%, and eosinophiles, from 2 to 4%, with toxic degenerative changes in all neutrophiles. Reticulocytes ranged from 4.4 to 7.2%; bleeding time (Duke), from 7 to 10 minutes, and the erythrocyte sedimentation rate, from 65 to 100 mm. per hour (Westergren). Clotting and prothrombin times were normal. Repeated urinalyses gave normal results. The reaction to the serologic test for syphilis (VDRL) was negative. Blood urea nitrogen values, cephalin-cholesterol flocculation, and the van den Bergh reaction were normal. The values for proteins varied from 6.48 to 6.40 gm., and those for globulin, from 3.48 to 3.43 gm., per 100 cc. of serum. The dextrose-tolerance curve was normal. Bacteriologic cultures of material from the ulcers grew mixtures of Staphylococcus aureus, a hemolytic Streptococcus, Proteus vulgaris, and Escherichia coli. A biopsy specimen

14. (*a*) Rogers and Langley.[13] (*b*) Peden, J. C.: Hypersplenism: 2 Cases with Leg Ulcers Treated by Splenectomy, Ann. Int. Med. **30**:1248, 1949.

Fig. 2 (Case 1).—Histologic section (same as in Fig. 2) showing chronic granulation tissue at the base of the ulcer. Hematoxylin-eosin stain; × 120.

Fig. 3 (Case 1).—Recalcitrant necrotic ulcer of lower left leg of man, aged 51 years, with Felty's syndrome.

of the bone marrow showed myeloid hyperplasia compatible with hypersplenism and the presence of the L. E. cell. Histologic examination of the skin and ulcers showed only chronic granulation tissue (Figs. 1 and 2). Roentgenograms of the chest and an electrocardiogram were normal. A histoplasmin skin test was negative.

Initial treatment consisted of 6,700,000 units of penicillin, compresses of a solution of copper and zinc sulfate, and dressings of lead oleate ointment (diachylon) and ointments of water-soluble chlorophyll derivatives (chloresium®). Despite treatment, three satellite bullae developed and ruptured, forming shallow purulent ulcers 2 cm. in diameter.

In May the patient exhibited a severe eruption of herpes zoster, involving the distribution of the fifth cranial nerve. Although the course was complicated by keratoconjunctivitis of the left eye, uneventful complete resolution occurred. In June another course of penicillin, 13,800,000

Fig. 4 (Case 2).—Chronic necrotic ulcer of lower left leg of woman, aged 52 years, with Felty's syndrome.

units, was given, in addition to 3% aureomycin ointment applied topically. The satellite ulcers healed in about six weeks except for one purulent necrotic lesion, measuring 4 by 6 cm., on the lateral portion of the left leg, which persisted unchanged until the date of discharge, Oct. 27, 1950.

When the patient was readmitted for reevaluation in May, 1951, the remaining ulcer on the left leg was essentially unchanged (Fig. 3). The leucocytes remained fixed at 1,000 to 1,200 cells per cubic millimeter. After one month's therapy with 0.5% neomycin ointment, the ulcer had reduced to 2.5 by 4 cm., and the patient was discharged to be managed on an ambulatory basis.

On several occasions splenectomy was advised; however, consent was refused by the patient.

CASE 2.—M. D., a white woman aged 52 years, had had severe rheumatoid arthritis for 11 years. She had had a gradual weight loss of about 10 lb. (4.5 kg.) and noticed a progressively

enlarging painless mass in the abdomen during the year prior to her admission to the Minneapolis General Hospital on Oct. 25, 1951. A nonhealing ulcer had been present on the left lower leg for six months.

There was an oval, sharply outlined, necrotic ulcer, measuring 5 by 6 cm., on the posterior surface of the left lower leg at the junction of the middle and lower thirds (Fig. 4). The lesion was granulomatous and partially covered by a sanguineopurulent crust. There were no evidences of venous or arterial insufficiency. The liver was palpable 5 cm. below the right costal margin. The spleen was firm, smooth, and nontender and was palpable 20 cm. below the left costal margin. There were chronic arthritic deformities of the joints of the hands, elbows, shoulders, knees, and feet. Multiple juxta-articular nodes were present on the extensor surfaces of both forearms. Results of the rest of the physical examination were noncontributory.

Laboratory studies of the blood showed hemoglobin content ranging from 8.3 to 9.9 gm. per 100 cc.; red blood cell counts, from 3,540,000 to 3,600,000, and leucocytes, from 650 to 1,200, with polymorphonuclear neutrophiles ranging from 4 to 16%, lymphocytes, from 79 to 88%, monocytes, from 3 to 4%, and eosinophiles, from 3 to 6%. The erythrocyte sedimentation rate was 112 to 127 mm. per hour (Westergren). The thrombocytes were fixed at 100,000, and a reticulocyte count was 3.2%. Bleeding, clotting, and prothrombin times were normal. Repeated urinalyses gave normal results. The reaction to the serologic test for syphilis (VDRL) was negative. Blood sugar, cholesterol, urea nitrogen, and the van den Bergh reactions were normal. The values for proteins varied from 6.4 to 6.48 gm., and for globulin, from 3.50 to 3.61 gm., per 100 cc. of serum. The dextrose-tolerance and sulfobromophthalein (bromsulphalein®) sodium tests gave normal results, but the cephalin-cholesterol-flocculation reaction was 4+. Bacteriologic cultures of material from the ulcer grew mixtures of Staphylococcus albus and Staph. aureus, Pseudomonas aeruginosa, diphtheroids, and a hemolytic Streptococcus. Blood cultures were sterile. A biopsy of the bone marrow showed myeloid hyperplasia and the presence of a few tart cells but no L. E. cells. Histologic examination of the skin and ulcer showed only chronic granulation tissue (essentially the same as in Figs. 1 and 2). Roentgenograms of the chest were normal.

Treatment consisted of compresses of a solution of protassium permanganate and dressings of 0.5% neomycin ointment. Splenectomy has been deferred because to date the patient's poor physical condition will not permit surgical intervention.

COMMENT

It is doubtful that Felty's syndrome is actually an entity; rather it seems to be a fortuitous coincidence of arthritis with some form of hypersplenism which causes a leucopenia. Arthritis is a chronic inflammatory (infectious) disease which has been shown to be a generalized process.[15] Splenomegaly, leucopenia, anemia, weight loss, liver dysfunction,[16] depression of the bone marrow, vasomotor abnormalities,[17] and fibrosis and atrophy of the skin have been found associated with arthritis. It is conceivable that ulceration of the skin could result from several of these factors; yet ulcers of the leg in rheumatoid arthritis alone rarely,[5d] if ever,[14b] occur. Hypersplenism may cause panhematopenia through a mechanism of increased destruction of blood elements and/or through "toxic" depression of the marrow.[18] Whether the arthritis and hypersplenism are independent processes or merely manifestations of a single etiological factor has been debated.[19] A variety of idiopathic hyper-

15. Hench.[5a] Hench and others.[8b]

16. Pemberton, R.: Arthritis and Rheumatoid Conditions, Philadelphia, Lea & Febiger, 1929.

17. Steinbrocker, O., and Sesit, M. F.: Chronic Rheumatoid Arthritis with Granuloma of the Spleen and Lymph Nodes in a Patient Presenting the Clinical Picture of Felty's Syndrome, New York J. Med. **40**:1795, 1940.

18. Hirschboeck.[4e] Peden.[14b]

19. Dawson.[5c] Curtis and Pollard.[9]

splenism described by Wiseman and Doan [20] as primary splenic neutropenia is defined pathologically by evidence of phagocytosis of granulocytes by the reticuloendothelial cells of the spleen. When this condition is associated with arthritis, it is clinically indistinguishable from Felty's syndrome; however, these authors admitted that the disorders may be separate entities. Curtis and Pollard,[9] Michael,[7b] and Dawson [5c] considered Felty's syndrome to be merely a variant of rheumatoid arthritis. They believed that the combination of arthritis, splenomegaly, and leucopenia is probably only a coincidence. Although the term is a convenient abbreviation for a symptom complex, they felt there is no justification for the segregation of these cases or for the use of the term.

The mechanism of the formation of leg ulcers in the cases presented is thought to be based mainly on the persistent leucopenia, because this was the most consistent manifestation throughout the clinical courses. Moreover, no evidence was found which suggested vascular or nutritional deficiency, specific granulomas, blood dyscrasias, or malignant growths. Only pathologic examination of the spleen could establish a relation with primary splenic neutropenia.

It is worthy of note that a few so-called L. E. cells were described as occurring in the bone marrow in Case 1. It has been suggested that some instances of "Felty's syndrome" may be cases of latent lupus erythematosus.[21] There were never cutaneous or visceral symptoms or signs suggesting a clinical diagnosis of lupus erythematosus in this case.

It is possible that the patients in this report would be benefited by splenectomy; this was not done because consents could not be obtained. The ulcers have improved gradually by conservative treatment, including support and topical antibiotic therapy. It is doubtful, however, that complete healing can be accomplished, because of the persistent leucopenias.

SUMMARY

Three cases of leg ulcers occurring in Felty's syndrome have been reported in the literature. Two additional cases are described.

Felty's syndrome probably is not an entity but a variant of rheumatoid arthritis which has an associated leucopenia due to hypersplenism.

Differential diagnosis of ulcers of the lower leg should include rheumatoid disorders associated with hypersplenism and leucopenia. Splenectomy should at least be of temporary benefit in cases of this type.

20. Wiseman, B. K., and Doan, C. A.: Primary Splenic Neutropenia: A Newly Recognized Syndrome Closely Related to Congenital Hemolytic Icterus and Essential Thrombocytopenic Purpura, Ann. Int. Med. **16**:1097, 1942.

21. Haserick, J. R.: Plasma, L. E. Test in Systemic Lupus Erythematosus: A Study of 23 Patients with a Positive L. E. Test, J. A. M. A. **146**:16, 1951.

Clinical Notes, New Instruments and Techniques

INTRAVENOUS CORTICOTROPIN THERAPY IN DERMATOLOGY

ROBERT H. PRESTON, M.D.
AND
LEON GOLDMAN, M.D.
CINCINNATI

Intravenous drip therapy with corticotropin has become increasingly popular in all fields of medicine since the work of Gordon [1] and Renold,[2] who showed the sustained value of this type of therapy. Its application to dermatology has been reported.[3] It is important to emphasize that there are in general three different types of daily intravenous drips: (1) the continuous (24 hours), (2) the intermittent (7 or 8 hours), and (3) the combined (Hampton), in which 10 mg. of corticotropin in 1,000 cc. of solution is given intravenously for 12 hours, then 10 mg. of corticotropin is administered intramuscularly.[4]

Advantages in the intravenous use of corticotropin are as follows:

1. The material and equipment needed to obtain results equal to, or better than, those with standard intramuscular uses are low in cost.

2. In some cases the intravenous drip therapy will stimulate the adrenal cortex when intramuscular therapy has failed because of partial or complete inactivation in muscle tissue.

3. Intravenously administered corticotropin is capable of reactivating the adrenal cortex suppressed by cortisone therapy after two or three days.[2a]

4. There are fewer side-reactions, since a small amount of the drug is being dispersed throughout the system slowly and steadily, a process which allows for continued absorption and hormonal response.

5. The dose equivalent is estimated variously from 4 to 6 to even 20 times the dose given intramuscularly.

The only disadvantages are the length of time that the patient must remain quiet for the intravenous administration and the occasional sensitivity reaction.

All the patients in this report were given the intermittent daily intravenous drip treatment with corticotropin in 500 to 1,000 cc. of 5% dextrose solution in water. In all our later work only 500 cc. was used routinely. The doses of corticotropin ranged from 10 to 25 mg. As a general rule, the dose is decreased with each subsequent injection. The number of injections varied in

From the Department of Dermatology and Syphilology, University of Cincinnati College of Medicine.

The corticotropin used in this study was furnished by R. C. Lemon, Pacific Laboratories, Inc., Richmond, Calif.

1. Gordon, E. S.; Kelsey, C., and Meyer, E. S.: Adrenal Stimulation by Intravenous ACTH, in Proceedings of the Second Clinical ACTH Conference, Vol. II: Therapeutics, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, p. 30.

2. (*a*) Renold, A. E.; Forsham, P. H.; Maisterrena, J., and Thorn, G. W.: Intravenously Administered ACTH: A Preliminary Report, New England J. Med. **244**:796-798 (May 24) 1951. (*b*) Shaw, C. C.: A Clinical Critique of ACTH and Cortisone, Mil. Surgeon **110**:42-50 (Jan.) 1952.

3. Editorial, Current News in Dermatology and Syphilology, Arthur G. Schoch, Dallas, Texas, Sept., 1951. Kanee, B.: Corticotropin (ACTH) Administered Intravenously, A. M. A. Arch. Dermat. & Syph. **65**:95 (Jan.) 1952.

4. Hampton, S. F.: Intravenous ACTH in the Treatment of Allergic Diseases, read before the American Academy of Allergy, Chicago, Feb. 20, 1952.

our series from 1 to 30 in a single course. The patients with lupus erythematosus required the prolonged treatment schedules. The first series included 25 patients: 5 with lupus erythematosus; 5 with penicillin reactions of the urticarial angioedema type; 4 having erythema multiforme; 2 having severe infectious eczematoid dermatitis (with concomitant antibiotic therapy); 2 with atopic dermatitis, and 1 each having sulfonamide reaction, barbiturate reaction (with encephalopathy), fixed drug reaction to antipyrine, dermatitis herpetiformis, mycosis fungoides (with concomitant high dosage of nitrogen mustard [methyl *bis* or *tris* (β-chloroethyl) amine hydrochloride]), psoriatic erythroderma, and pyoderma gangrenosa. A patient with a fixed drug eruption to antipyrine was given 10 mg. of corticotropin intravenously by drip during a stage of remission. Three hours after treatment had started, 3 grains (0.19 gm.) of antipyrine was given orally. This dosage had caused a bullous flare-up in the past. The patient complained of bilateral pruritus of the hands one hour after the antipyrine was given; 12 hours later the temperature was 104.5 F., although 10 mg. also had been given intramuscularly shortly before. All signs and symptoms disappeared during the next 24 hours while intravenous drip therapy and intramuscular administration of 10 mg. of corticotropin at bedtime were continued. On the third day therapy was discontinued, and the patient then had a delayed and severe bullous reaction. This delayed response of a fixed drug eruption is interesting in the light of the report we gave of an antipyrine-sensitive patient protected by cortisone (cortone®) acetate.[4a] There were no children in this preliminary series, although corticotropin may be given intravenously to children also.

As others have indicated, this type of therapy should be limited generally to the acute severe dermatological conditions of hypersensitivity. It has been suggested as a procedure for the relief of pruritus. We agree with Rothman [5] that relief of pruritus can be secured with corticotropin therapy if a local inflammatory reaction is causing the pruritus and if this local inflammation is relieved.

In some instances, controls were needed, as in atopic dermatitis in which the subjective response was just as good when dextrose drip without the corticotropin was substituted in the course of therapy. In his study of asthma Arbesman used, as control, placebo dextrose drip for three days before corticotropin was added, unknown to the patient.[6] In short-time treatment procedures (three or four days) there is little chance of inducing refractoriness to corticotropin. In our patients there was no post-treatment exhaustion syndrome, for in our long series cortisone was given concomitantly. There was, likewise, no evidence of sensitivity to the corticotropin. The only patient in the series in whom phlebitis developed was one with lupus erythematosus.

Because of the rapid excretion of corticotropin following intravenous use, this technique cannot be employed as an occasional therapy for ambulatory patients. At present, an attempt is being made to set up a routine type of technique for ambulatory patients. The outpatient given cortisone orally also receives corticotropin intravenously twice a week. This appears to be of value, for example, in lupus erythematosus, when adrenal stimulant therapy is needed during the course of prolonged steroid therapy.

The intravenous administration of corticotropin in the acute severe dermatological reactions of hypersensitivity may serve, as it were, as a clinical test for rapid evaluation of activity (biological assay) of the corticotropin product.

Since this is corticotropin therapy, even for short-term courses the simple clinical procedures of checking body weight and blood pressure can be followed. Potassium chloride, 3 gm. daily, may be given if indicated. It is, however, a safer procedure to use it routinely even in the short-term courses. We have not used potassium chloride in the actual drip. Studies have been initiated on administration of compound F by intravenous drip technique.

4a. Goldman, L., and Rockwell, E.: Prevention of Hypersensitivity Reaction to Drug with Simultaneous Administration of the Drug and Cortone,® A. M. A. Arch. Dermat. & Syph. **64**:644 (Nov.) 1951.

5. Rothman, S.: Personal communication to the authors.

6. Arbesman, C. E.; Schneider, M.; Greene, D., and Osgood, H.: Intravenous ACTH for Bronchial Asthma, read before the American Academy of Allergy, Chicago, Feb. 20, 1952.

CONTACT DERMATITIS DUE TO "QUOTANE"

JOHN F. DALY, M.D.
BURLINGTON, VT.

The search for safe and effective antipruritic agents has led from time to time to the introduction of many agents of widely varying chemical composition and differing degrees of cutaneous sensitizing properties. The sensitizing potential of most of the surface-active local anesthetic drugs is so well known as to require no comment. In a recent issue of the A. M. A. ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY, Bereston[1] reported an instance of sensitization to crotamiton (N-ethyl-o-crotonotoluide; eurax®). In the same issue of this publication, Lynch and Ockuly[2] reported a clinical study of the topical use of 1-(β-dimethylaminoethoxy)-3-n-butylisoquinoline monohydrochloride ("quotane") for the relief of itching in a variety of dermatoses. They reported 258 clinical trials in 195 patients in which they encountered only 1 patient who presented an acute reaction resembling contact dermatitis, and by patch testing it was traced to sensitization to the vehicle and not to the drug itself.

Inquiry to the makers of "quotane"[3] elicited the information that a total of more than 3,000 patients have been tested with "quotane" lotion and ointment. Of this total only nine cases of possible sensitization have been observed, and only one of these was proved to be due to the drug itself. Though the index of sensitization thus seems low, the report of a definite case of cutaneous sensitization to such a potentially widely used preparation seems warranted.

REPORT OF A CASE

Mrs. D. S., a 45-year-old white housewife, had an itching dermatosis of both axillae in October, 1950. When first seen in January, 1951, she presented a localized neurodermatitis of both axillae. Topical therapy of various sorts and a total of 550 r of unfiltered x-rays given in eight doses over a period of about 12 months gave only temporary and unsustained relief. On Oct. 2, 1951, the patient reported with a recurrence of itching of four weeks' duration and with only slight local signs of the neurodermatitis. "Quotane" lotion was given for topical application as needed to control itching. In two weeks the itching had increased rather than decreased, and a fine, red papular eruption had appeared. The axillae were quite dry, and "quotane" ointment was substituted for the lotion, which has proved very drying. Two weeks later the eruption had regressed, and itching was satisfactorily controlled. Though itching continued it was better controlled than by any other topical preparation. On Dec. 6, 1951, swelling, redness, and the appearance of fine vesicles in the axillae were noted by the patient. On Dec. 14, the patient presented a typical contact dermatitis of the axillae, extending to the posterior axillary folds, the arms, and the breasts. A patch test using the "quotane" ointment was applied to an uninvolved area of the skin on the medial aspect of the right arm. After 30 hours the local discomfort at the patch-test site was so intense that the patient removed the patch. When she was seen on Dec. 17, the patch-test site showed a 3+ response, and the dermatitis had extended to involve the forearms and much of the anterior surface of the chest and breasts, as well as the neck. She was hospitalized on Dec. 17, and by Dec. 23 the dermatitis had subsided sufficiently to permit her discharge. Treatment consisted in the application of compresses of 1:60 Burow's solution (aluminum acetate solution) and a simple shake lotion. Closed patch tests applied on Jan. 29, 1952, to the base of the "quotane" ointment[4] and to 1:1000 tincture thimerosal N. F. (the latter is used as a pre-

Associate Professor of Dermatology and Chairman, Division of Dermatology, College of Medicine, University of Vermont.

1. Bereston, E. S.: Contact Dermatitis Due to N-Ethyl-o-Crotonotoluide (Eurax®), A. M. A. Arch. Dermat. & Syph. **65**:100 (Jan.) 1952.

2. Lynch, F. W., and Ockuly, O. E.: Clinical Study of "Quotane," A. M. A. Arch. Dermat. & Syph. **65**:35 (Jan.) 1952.

3. Members of the Medical Department, Smith, Kline & French Laboratories, Philadelphia: Personal communication to the author.

4. The material used in this test was supplied by Smith, Kline & French Laboratories, Philadelphia.

servative in "quotane" ointment) caused no cutaneous reaction after an application of 48 hours. It thus appears that the 1-(β-dimethylaminoethoxy)-3-n-butylisoquinoline monohydrochloride was in fact the sensitizing agent.

SUMMARY

A case of contact dermatitis due to the antipruritic preparation 1-(β-dimethylaminoethoxy)-3-n-butylisoquinoline monohydrochloride ("quotane") is reported.

135 College St.

PITYRIASIS ROSEA

MILTON S. HARTMAN, M.D.
BROOKLYN

I am submitting this report of a case of pityriasis rosea because of the following unusual features: (1) a second attack; (2) the long period of time elapsing between the appearance of the herald patch and the general eruption (24 days); (3) the unusual location of the herald patch (forehead), and (4) the unusual characteristics of the herald patch.

REPORT OF A CASE

H. D., a housewife aged 28, first appeared for treatment in February, 1948, presenting a typical eruption of pityriasis rosea. The general eruption had occurred two weeks previously, following by one week the appearance of a herald patch on chest. All lesions cleared within six weeks, during which period ultraviolet irradiation was administered once or twice weekly.

She again appeared in November, 1951, with another typical eruption of pityriasis rosea, except for an atypical lesion on the right side of the forehead at the hairline. This was a rounded, erythematous, smooth, considerably elevated, nickel-sized (2.2-cm.) nodule, almost cystic in appearance. It had appeared 24 days before the general eruption, which had been present for one week. At no time in the course of the eruption did this lesion become scaly. It disappeared with the other lesions after three weeks' therapy with ultraviolet irradiation given twice weekly.

COMMENT

While the afore-mentioned features may not be too unusual in different cases, their concurrence in the same person is worthy of note.

Of special interest seemed to be the nature of the herald patch in the recurrence, that is, its marked elevation and the total absence of scale.

One may argue that perhaps this was not the herald patch at all, but a concomitant lesion; but its course, its gradual flattening out and disappearance along with the rest of the eruption, makes such a surmise untenable.

711 Bushwick Ave. (21)

USE OF ATTENUATED OR INACTIVATED AUTOGENOUS BLOOD SERUM IN MANAGEMENT OF PEMPHIGUS VULGARIS

Report of a Case

C. P. BONDURANT, M.D.
OKLAHOMA CITY

Mrs. E. M. M. was admitted to the University Hospital May 11, 1951, with a progressive bullous eruption involving the left eyelid, trunk, arms, and legs, with marked lesions in the inguinal region. The case was studied in routine form from the clinical and laboratory stand-

Fig. 1.—Patient with pemphigus vulgaris on May 22, 1951, before treatment was started.

Fig. 2.—Patient with pemphigus vulgaris after therapy, on Sept. 28, 1951.

point. A biopsy was done on May 22, 1951, and was reported as revealing acute pemphigus vulgaris. Figure 1 shows the patient on this date. Treatment was started with the use of the patient's own blood serum, prepared and given in the following manner: Thirty to 35 cc. of blood was drawn at weekly intervals under aseptic conditions; the blood was refrigerated overnight and centrifuged; the serum was drawn off and heated in a hot water bath at 56 C. for 35 minutes. Care was taken not to exceed the temperature of 56 C., as serum is coagulated at 60 C. This inactivated or attenuated serum was given intramuscularly in daily doses of 5 cc. each. Thirty such doses were given this patient. Because of a severe "chest cold" she was given three doses of penicillin and vitamin therapy. Improvement in the skin was noted on the eighth or ninth day following institution of treatment. The patient steadily improved in both her skin picture and her general health, as shown by the clinical photographs.

PLASTIC DIASCOPE FOR DERMATOLOGY

LEON GOLDMAN, M.D.
AND
RAYMOND SUSKIND, M.D.
CINCINNATI

For many years a curved glass diascope has been used by dermatologists in Europe. In this country the inconvenient rectangular piece of glass or, more frequently, the less suitable microscopic slide is used as a diascope. The European-type diascope has been modified so that it can be made from clear plastic and so that it is more efficient for the examination of curved areas. The angles of curvature are made a bit different in order to reach areas of the face, such as the sides of the nose and the orbital ridges, and the tips and sides of the fingers. The diascope is

Plastic diascope.

approximately 15 cm. long, 1.3 cm. across one end, and approximately 2.3 cm. across the other end. Curvatures are given for each end. The diascope is made of plastic which can be cleansed easily with alcohol. Unlike the glass diascope it does not break when it is dropped. However, it cannot be bent too much without breaking, and it can be scratched. Scratched areas may be polished with talc or cigarette ash. The edges are marked off in millimeters to assist in measuring sizes of lesions. Efforts to devise a surface thickness to provide some degree of magnification were not practical. Attatchment to an illuminating source is not necessary. The diascope can also be used as a tongue blade, and it can be carried conveniently in the pocket.

From the Department of Dermatology and Syphilology of the College of Medicine of the University of Cincinnati.

The plastic diascope was made by CGS Company, Box 1111, Cincinnati 2, Ohio.

ALOPECIA AREATA UNIVERSALIS

Results in One Case of Treatment with Corticotropin (ACTH) and Cortisone Acetate Intramuscularly and Post-Treatment Observations

CHARLES K. WAINGER, M.D.
AND
WILLIAM P. CAPPLEMAN, M.D.
TEMPLE, TEXAS

Dillaha and Rothman [1] have recently reported on the treatment of four patients having alopecia areata totalis and universalis with cortisone acetate. Three of their four patients responded to oral cortisone acetate therapy. At the time of writing, all three of these patients were still receiving treatment.

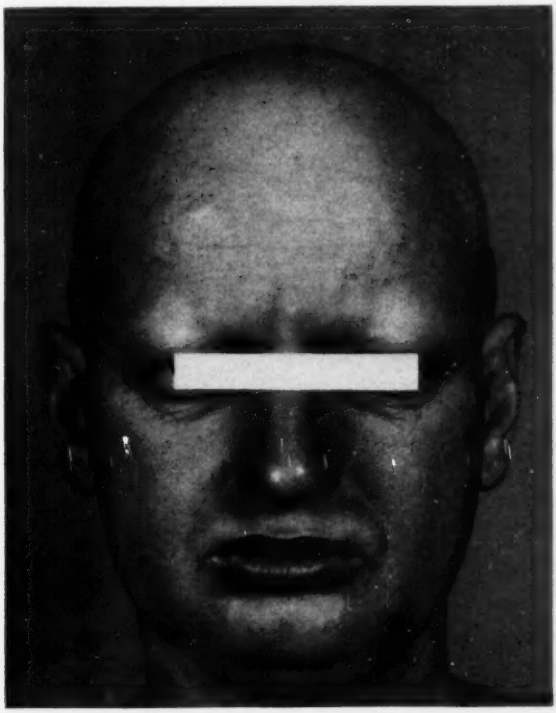

Fig. 1.—Patient with alopecia areata universalis as seen on first examination Aug. 9, 1951.

From the Section of Dermatology and Syphilology of the Medical Service of the Veterans Administration Center, Temple, Texas.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Dillaha, C. J., and Rothman, S.: Treatment of Alopecia Areata Totalis and Universalis with Cortisone Acetate, J. Invest. Dermat. **18**:5-6 (Jan.) 1952.

The following case of alopecia areata universalis is being reported after having been under observation for seven months. During this time the patient received two courses of corticotropin (ACTH) and one course of cortisone acetate intramuscularly. Observations made after these were discontinued are also reported.

REPORT OF A CASE

H. C., a 36-year-old post-office clerk, was first seen in August, 1951. He gave a history of having first noted circular patches of alopecia in the occipital region in 1943. About five months after the onset there was regrowth of hair in these areas of alopecia coincident with his receiving a series of injections of anterior pituitary extract. In 1945 patchy alopecia of the

Results Obtained in a Patient with Alopecia Areata Universalis Treated with Corticotropin and Cortisone Acetate Given Intramuscularly and Post-Treatment Observations

Dates	Treatment	Observations
Aug. 14 to Sept. 11, 1951	ACTH intramuscularly, 100 mg. daily	First evidence of regrowth of hair was noted on scalp, eyebrows, and bearded region of face within 14 days of beginning treatment; at end of this period there was continuing growth of hair in these areas, (Fig. 2), and some regrowth of hair in presternal and pubic regions; there was no regrowth of hair in axillae
Sept. 11 to Oct. 29, 1951	ACTH discontinued	Three weeks after stopping ACTH therapy, small circular patches of alopecia were noted in occipital region (Fig. 3); these areas progressively increased in number and size; 6 wk. after ACTH therapy had been stopped, there was marked patchy loss of hair over entire scalp, of eyebrows, and of upper lip; the remainder of bearded area of face was, as yet, not affected, this area continuing to show even growth of hair
Oct. 29 to Dec. 4, 1951	Second course of ACTH intramuscularly; initial dose 40 mg. a day, gradually increasing to maximum dose of 100 mg. a day; maximum dose maintained for 2 wk.	No further loss of hair was noted after daily dose of 60 mg. was reached; throughout this period hair remaining on scalp and face from first course of ACTH continued to grow luxuriantly, but there was no new growth of hair in extensive patches of alopecia on scalp (Fig. 4); there was incomplete regrowth of hair on upper lip and eyebrows; sparse hairs in presternal and pubic regions persisted
Dec. 1 to Dec. 13, 1951	Cortisone acetate, intramuscularly, 100 mg. daily	No change in hair growth; hair already present continued to grow, but patches of alopecia on scalp showed no regrowth of hair
Dec. 14, 1951 to March 6, 1952	ACTH and cortisone therapy discontinued	Six weeks after discontinuance of therapy, remaining scalp hair began to fall out; there was also the beginning of thinning of eyebrows and hair of bearded area of face; this hair loss continued, and at end of this 12-wk. period of observation there was almost complete regression to original total alopecia of head (Fig. 5); sparse regrowth of hair in presternal and pubic regions was still present unchanged

scalp again developed. On this occasion the alopecia progressed to involve all the body hair. Some hair was still present on the scalp until the summer of 1950. This was the last to disappear, with resulting universal alopecia.

Examination showed that, except for about 10 hairs on the vertex of the scalp and single long, fine hairs over the occiput, behind the ears, and in the right axilla, there was universal alopecia (Fig. 1).

The patient was treated with corticotropin and cortisone acetate given intramuscularly and was followed from Aug. 15, 1951, to March 6, 1952. The accompanying table shows the results obtained in this case.

COMMENT

Corticotropin was effective in causing regrowth of hair in this patient with universal alopecia areata. Growth of hair was also maintained with cortisone acetate given intramuscularly.

First evidence of regrowth of hair occurred on the face and scalp within 14 days after the start of corticotropin treatment and was progressive as long as corticotropin and cortisone were administered.

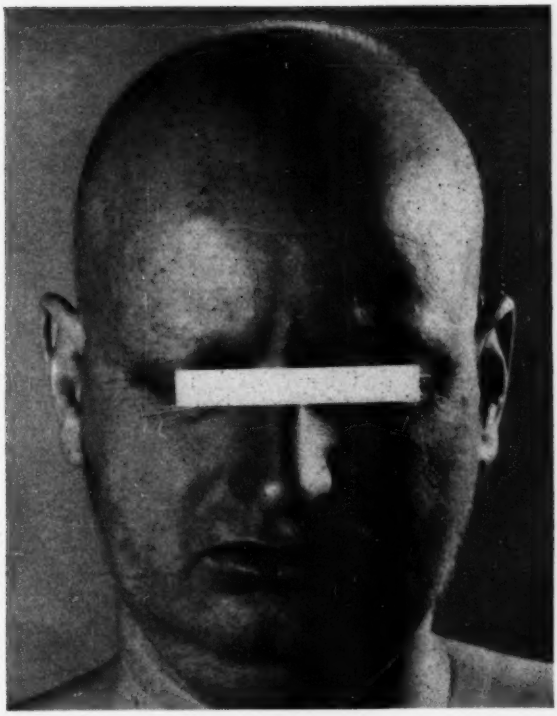

Fig. 2.—Sept. 13, 1951. Regrowth of hair on face and scalp after four weeks of corticotropin given intramuscularly in dosage of 100 mg. a day.

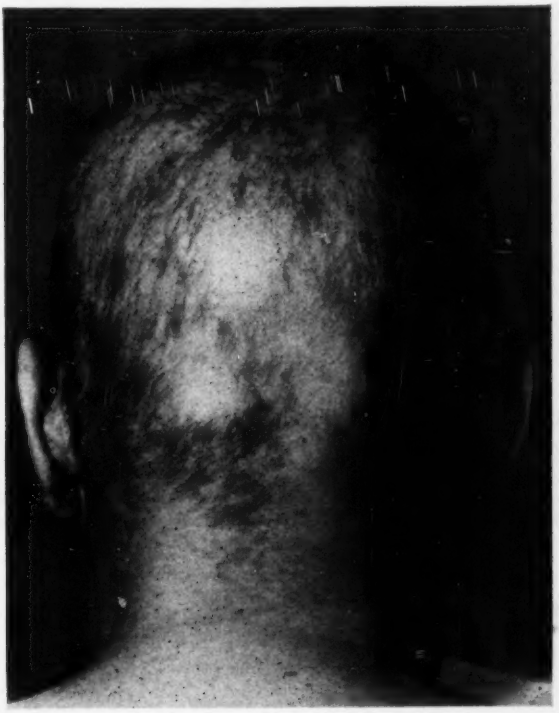

Fig. 3.—Oct. 8, 1951. Beginning patchy loss of hair in occipital region four weeks after corticotropin therapy was stopped.

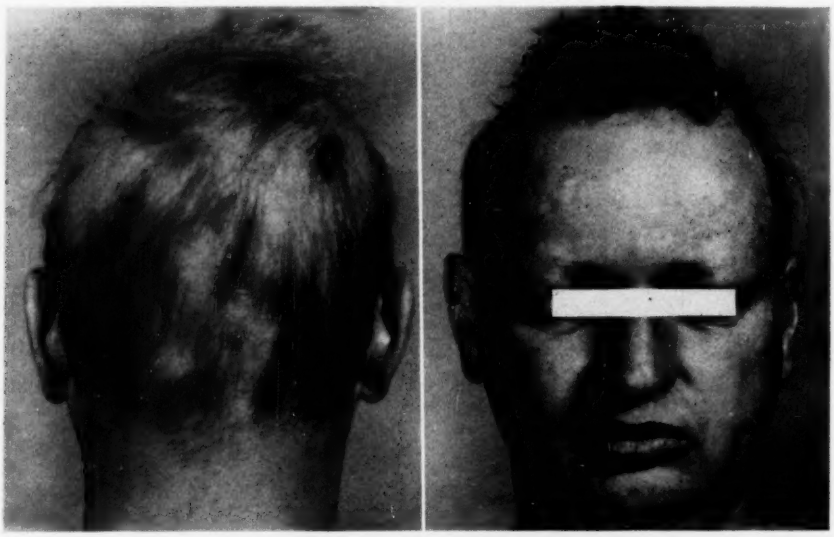

Fig. 4.—Dec. 14, 1951. Left, persistence of patchy alopecia of scalp after second course of corticotropin and a course of cortisone acetate given intramuscularly. Hair remaining from regrowth on first course of corticotropin shows continuing growth. Right, front view.

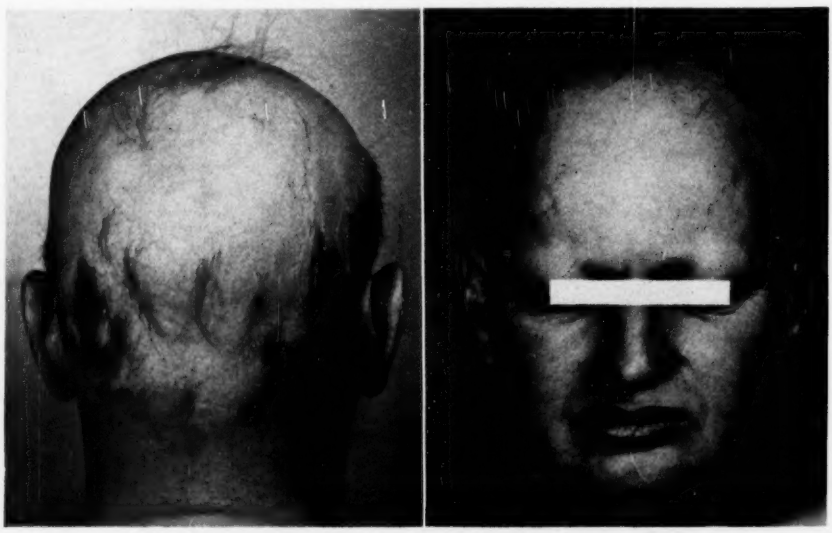

Fig. 5.—March 7, 1952. Left, progressive loss of hair previously regrown, 12 weeks after corticotropin and cortisone acetate therapy were discontinued. Right, front view.

Three weeks after completion of the first course of corticotropin therapy there was beginning loss of the hair previously regrown, starting as round patches of alopecia in the occipital region. These areas progressively increased in number and size. This form of hair loss resembled that seen in alopecia areata. Hair loss was noted six weeks after a second course of corticotropin, followed by one of cortisone.

At the end of our 12-week post-treatment period of observation there was almost complete loss of the hair which had previously regrown on the scalp and face.

It should be emphasized that the results and observations noted in this report are those obtained in only one patient.

LEUCODERMA OF PENIS FROM CONTACT WITH RUBBER

JOHN GODWIN DOWNING, M.D.
BOSTON

Depigmentation of the skin from contact with rubber has been reported on various occasions since the original descriptions by Oliver and his associates.[1] In these cases depigmentation of

Depigmentation of glans penis from use of rubber condoms.

1. Oliver, E. A.; Schwartz, L., and Warren, L. H.: Occupational Leukoderma, J. A. M. A. **113**:927-928 (Sept. 2) 1939. Schwartz, L.; Oliver, E. A., and Warren, H. L.: Occupational Leukoderma, Pub. Health Rep. **55**:1111-1130 (June 31) 1940. Oliver, E. A.; Schwartz, L., and Warren, L. H.: Occupational Leukoderma, Arch. Dermat. & Syph. **42**:993-1014 (Dec.) 1940.

the skin of the hands and arms was seen in 20 men employed in a tannery. They wore a very heavy gauntlet type of rubber glove. After a thorough investigation, including patch tests of all the affected persons, it was discovered that an antioxidant added to the rubber for the purpose of improving its aging properties was the cause. This antioxidant was known by the trade name "agerite alba" and was said to be the monobenzyl ether of hydroquinone.

Other writers [2] have reported similar cases. I have seen this type of depigmentation in the axillae in women, as a result of the wearing of rubber dress shields. I have also seen it on the hands of workers contacting rubber containing this compound. The following case, however, is the first in which I have seen it occur on the penis.

REPORT OF A CASE

C. V. S., aged 28, was referred to me by his physician for advice regarding white patches on his penis. Examination showed depigmentation spreading out from the median groove on both sides of the glans penis. It was most marked on the under-surface. Otherwise the mucous membrane was normal. Examination of the entire skin revealed no other patches of depigmentation. His history revealed that he had been using rubber condoms for six years.

2. Spencer, G. A.: Leukoderma Produced by Antioxidants: Report of Cases, Arch. Dermat. & Syph. **58**:215-219 (Aug.) 1948. McNally, W. D.: Depigmentation of Skin by Rubber Gloves, Indust. Med. **8**:405-410 (Oct.) 1939. Zakon, S. J., and Goldberg, A. L.: Occupational Leucoderma from Rubber Dust and Debris, A. M. A. Arch. Dermat. & Syph. **64**:441-443 (Oct.) 1951.

ESTROGENS IN TREATMENT OF ACNE VULGARIS

WILLIAM H. GOECKERMAN, M.D.
AND
LOUIS F. X. WILHELM, M.D.
LOS ANGELES

In 1950 one of us (W. H. G.) [1] called attention to the very excellent results he had obtained by the estrogen treatment of acne vulgaris in the female over a period of more than eight years. Since then both of us have continued use of estrogens systematically with the same brilliant results. At the time we first called attention to the great value of the estrogens in the treatment of acne, our findings contrasted strikingly with the opinions generally entertained by good dermatologists, although there were publications which claimed moderately good results. In the meantime the estrogens evidently have been freely tried, but it would seem, judging from personal communications received and articles published, that the results of most observers have been rather indifferent. The inconsistent results 10 years or more ago are possibly explained by the lack of proper potency in the estrogenic preparations, but this explanation would hardly hold for the recent products. It seems to us, therefore, that only the method of administration can be blamed for the indifferent results. While we wish to emphasize that no type of routine administration will yield consistently good results and that each patient is more or less a law unto herself, we will endeavor to describe our procedure as best we can.

In years past we have treated acne, as have most dermatologists, by multiple attack. Allergens, vitamin deficiency, focal infections, unsuitable diet of various types, low-grade tuberculosis, etc., were carefully considered. Of course, treatments involving x-rays, local manipulations, vaccines, and topical applications were routine. All this we have, in the main, discarded. The factor of psychotherapy, which is such an important element in the management of many disease processes, probably cannot be entirely eliminated. It is true that we take a

1. Goeckerman, W. H.: Hormonal Therapy of Acne Vulgaris in the Female: A Clinical Attempt at Its Evaluation, Arch. Dermat. & Syph. **61**:237-241, 1950.

very positive attitude toward the patient when discussing our treatment with her. It is not likely, however, that this would play a predominant role in our consistently good results. We have treated all types of acne vulgaris, as some textbooks refer to them, the simplex, the punctata, the papulosa, the pustulosa, etc. They all have responded equally well. Treatment must be adequate, though the amount may differ considerably in individual patients. During the course of therapy dosage should not be excessive. It would seem that a certain balance must be obtained. Since we do not know just how the estrogens exert their effect, we can best judge the result by observing the behavior of the acne clinically. After a little experience, this can be done easily; in fact, the patient usually volunteers her own opinion regarding its behavior. We are convinced that estrogens do not merely neutralize or counteract an excess amount of the male factor. It is far more likely that they stimulate every glandular organ in the body; hence the results obtained may be compared with the effect of cortisone and corticotropin (ACTH) in a variety of disease processes.

As yet we have no laboratory procedures which can guide us effectively in the practical use of estrogens. Over the last 10 or 11 years we have administered the estrogens in the form of diethylstilbestrol, water-insoluble estrogenic substances (amniotin®), estradiol, conjugated estrogenic substances (premarin®), ethinyl estradiol (estinyl®), estrone (theelin), and estriol (theelol). All of them have been therapeutically effective, but not equally effective in all patients. At first the dose is always the smallest accepted as a therapeutic dose, and then it is increased as judgment indicates from the effect on the patient and the acne. It is frequently necessary to reduce the dose somewhat after the patient has been under treatment for some time. Treatment is continuous if well tolerated. Minor interference with menstruation is ignored, but excessive flow indicates immediate discontinuance of the hormone therapy. After a rest period, the same dose often can be resumed without discomfort. While some patients require very large doses, in most instances they are not necessary; in fact, excessive dosage may aggravate the acne. While local applications of estrogens no doubt have some beneficial effect, in our investigation we were concerned chiefly with their evaluation on internal administration. In the last four or five years we have used ethinyl estradiol, conjugated estrogenic substances, and water-insoluble estrogenic substances almost exclusively. We are unable to say whether these preparations are superior in their effect to the others, but they have been very effective and have produced little or no discomfort and few or no undesirable side-effects in the patient.

Our experience with estrogens in the treatment of acne in the male has been too limited for us to express an opinion. While we have some evidence that they are of value, our approach has been very cautious, partly because there may be some real danger of damage to the male and partly because at present such treatment probably has a medicolegal aspect. This problem, however, merits further investigation.

UNUSUAL DISTRIBUTION OF CHICKENPOX LESIONS

FRANK C. COMBES, M.D.
AND
MICHAEL J. SCOTT, M.D.
NEW YORK

During the physical examination of a patient under treatment for psoriasis, an interesting observation was made. The patient had recently acquired chickenpox (varicella), and it was noted that chickenpox lesions occurred almost without exception in the sites of former psoriatic patches.

REPORT OF CASE

An 8-year-old Caucasian boy was initially seen in 1946 with generalized psoriasis. It had been present since the age of 6 months. He was observed at intervals from 1946 to 1951. In

October, 1951, the lesions were in a stage of partial remission. In addition, however, typical vesicopustules of chickenpox were distributed almost solely on the sites of the psoriatic lesions undergoing involution. The vesicles contained clear fluid and varied from 1 to 5 mm. in diameter. Many lesions were on an erythematous base. Some showed central umbilication. Neither the

Left shoulder area, showing chickenpox lesions in resolving psoriatic patches.

patient nor any of his associates had been vaccinated recently against smallpox. Slight malaise was the only symptom.

COMMENT

The interpretation of this case, or, indeed, of the factors determining the distribution of chickenpox lesions in any case, is problematic. A possible explanation is that psoriasis offered a locus minoris resistentiae to the invading virus.

Correspondence

DERMATITIS AND ECZEMA

To the Editor: I should be glad if you would open your columns to a discussion on the terms dermatitis and eczema, with a view to arriving at a better understanding of the use of these terms in the field of dermatology. I make this suggestion because all dermatologists know how large a proportion of their cases can be placed under one or other term.

At the Kingston Public Hospital, Jamaica, when all patients with diseases of the skin were being referred to the Skin Department, the three commonest dermatoses in 6,740 new cases seen by me were the following:

	No. of Cases	%
Fungous infections (all types)	779	11.5
Eczema (a specific dermatosis; all types as defined herein)	570	8.5
Dermatitis (a nonspecific dermatosis)	361	5.35

At present, with those having only the more intractable conditions being referred, the incidence of dermatitis and eczema among my patients has risen to 12 and 8%, respectively. The last percentages can be taken to denote a trend only, as the numbers involved are very much smaller.

While some dermatologists consider the terms dermatitis and eczema interchangeable, others would abolish the term eczema and speak of dermatitis of external origin and dermatitis of internal origin. Other terms suggested are eczematous dermatitis, or dermatitis venenata or sensitization (or contact) dermatitis and dermatitis medicamentosa, on the one hand, and atopic dermatitis, neurodermatitis disseminata, constitutional eczema, and postinfective (or posttraumatic or flexural or bacterial) eczema, on the other hand.

I wish to plead (1) for retention of the term eczema for that specific type of reaction occurring in the epidermis as a result of the interaction of some foreign substance (or antigen) with antibodies to that particular antigen; (2) that the term dermatitis be reserved for all inflammatory reactions in which the antigen-antibody interaction is not definitely established, and (3) that the terms be considered neither interchangeable nor synonymous.

Eczema is derived from the Greek ἐκ (out) and ζέω (boil): ἐκζεῖν, to boil out or break out. The use of the term is one of great antiquity. The picture which it conveys of a pot boiling with little bubbles coming to the surface is an accurate representation of the eczema picture, histologically. For these two reasons alone there is much to be said for retention of the term eczema. The term has come to represent a dermatosis which is a development (or complication) of preceding nonspecific dermatitis.

The tendency to develop the complication eczema is a constitutional one and differs from person to person, qualitatively and quantitatively. After some insult (from external or internal source), a local nonspecific reaction or dermatitis may result. This nonspecific reaction is demonstrable histologically, and the changes caused by it are not necessarily irreversible. In a minimum of 7 to 10 days antibodies to the particular foreign substance (or antigen) will develop in those persons so constitutionally predisposed. The antibodies seem to become fixed in or on cells of some areas of the epidermis. A permanent (i. e., irreversible) change occurs which is not demonstrable histologically. The reaction is a type of defense phenomenon. When further insults from the same or related antigens occur, the tissues with antibody bear the full brunt of the insult and prevent the antigen from spreading readily to other parts of the body. The effect is thus localized, but the local reaction may be particularly intensified and bears little relation to the amount of antigen obtaining access to the body after the first insult. It could be, however, that the intensity of the reaction bears some relation to the amount of antibody present. (In the nonspecific [reaction] dermatitis the intensity of reaction for any given person seems to bear some quantitative relation to the offending substance involved.) Without the further insult or ingress of antigen, no eczema reaction can occur. Thus, there may be a short or long period before the eczema reaction can take place, or there may be complete freedom from it in the absence of further attack by antigen.

Dermatitis should refer to all inflammatory reactions of the skin not including eczema. The reaction may be such as is to be expected from insults to the average normal skin. The cause is then usually fairly obvious and the harmful agent (physical or chemical) may be placed before the term dermatitis, e. g., solar dermatitis or poison-ivy dermatitis. On the other hand, a reaction may be produced that is quite unexpected, or, at least, not expected in the average skin. This is the type more frequently met with in practice, and its cause is often very difficult to determine. It is a nonspecific reaction of a skin hypersensitive to substances which do not normally produce any reaction. When the cause is known, it should be sufficient to place the cause before the dermatitis, e. g., chrome-dye dermatitis or arsenical dermatitis. When the cause is obscure, terms such as dermatitis venenata or contact dermatitis or dermatitis medicamentosa (from drugs taken internally) may be used to express the diagnosis.

Every dermatologist is familiar with the condition of stasis (or varicose) dermatitis, but if, as a result of poor circulation through varicose veins, an unhealthy condition develops on the devitalized skin of the legs, infection is apt to be superimposed—perhaps following minor trauma—and may persist and progress. Antibodies to the infective organisms or to products from broken-down tissue may develop. Interaction between antibodies and allergen will produce an eczema superimposed on a dermatitis. It is, therefore, correct to speak of varicose eczema for this new development, but, to avoid confusion, I should suggest that the term postinfective or post-traumatic eczema on varicose or stasis dermatitis be used.

It seems that final general agreement by dermatologists on the use of the terms dermatitis and eczema to denote two different types of reaction in the skin should not be difficult to obtain.

H. D. Chambers, M.D., Jamaica, B. W. I.

Kingston Hospital.

CORRECTION

The president of the Chicago Dermatological Society is now Dr. James R. Webster, 55 E. Washington St., rather than Dr. Theodore Cornbleet, as was stated in the Directory of Dermatologic Societies in the July issue, page 142.

Society Transactions

CLEVELAND DERMATOLOGICAL SOCIETY

George H. Curtis, M.D., *President*

John R. Haserick, M.D., *Secretary*

Harold N. Cole Jr., M.D., *Reporter*

Nov. 29, 1951

Lymphocytic Lymphosarcoma. Presented by Dr. H. H. Bremers, Dr. C. George, and Dr. C. Sunit, for Dr. David Rosenberg.

F. K., a white man aged 52, has noticed recurrent nontender lumps in the skin for the last two months. About two weeks prior to admission he noticed a large mass in the left parotid area, a steady left retro-orbital pain, and diplopia.

On physical examination, a bony prominence in the frontal area, nodules in the skin of the right and left frontal areas, and a movable tumor which was attached to the skin in the left parotid area were noted. There was a slightly indurated area in the skin of the right anterior chest wall. A small nodule was present in the skin over the right biceps. There was generalized adenopathy. A left posterior cervical node and a mass in the right inguinal area were particularly prominent. The patient was unable to open the left eyelid. The left pupil was somewhat dilated but reacted to light. There was loss of medial, superior, and inferior gaze of the left eye. Diplopia was noticed of objects to the right of center.

The urinalysis gave normal results. The blood urea nitrogen was 12 mg. per 100 cc. The total serum proteins were 6.5 gm. per 100 cc., with an albumin-globulin ratio of 2.3. The hemoglobin concentration was 14.2 gm. per 100 cc., with 4,700,000 red blood cells and 8,000 white blood cells per cubic millimeter, and 78 segmented neutrophiles, 6 unsegmented neutrophiles, 11 lymphocytes, 4 monocytes, and 1 eosinophile per 100 cells. The observed and corrected sedimentation rate was 11 mm. per hour. A blood serologic test was negative. The spinal fluid pressure was 160/100, with normal dynamic pressure; cell count revealed 2 monocytes. The Pandy reaction was 1 +. There were 40 mg. per 100 cc. of protein and 118 mEq. per liter of chloride.

Roentgenograms revealed a normal chest and a normal skull.

A left supraclavicular node and a left epitrochlear node were excised. Histologic examination of these nodes showed that their follicular pattern was nearly obliterated by compact sheets of small cells which invaded the capsule. Cell borders were indistinct, and cytoplasm was scant. There was little variation in cell size. The nuclei were oval for the most part, but some were irregular in outline. There was moderate variation in nuclear size. Many were hyperchromatic. Nuclear chromatin was finely granular. Mitotic figures averaged 4 per high-power field. There were a few large oval, pale-staining nuclei with nucleoli.

Roentgen therapy was started on Nov. 23, 1951, to the base of the skull, both axillae, and both inguinal areas. A course of 2,500 r to each area is contemplated by the roengenologists. The skin lesions have regressed considerably, and the hypertrophied lymph nodes are smaller.

DISCUSSION

Dr. H. H. Johnson: I think the way these lesions have regressed in the last week is remarkable. The patient had an infiltrated, yellowish-red plaque, about 2.5 cm. in diameter, on the left cheek. Today one can see only a little scale and erythema where it had been. I did not know whether it was a granuloma or an infiltrate from Hodgkin's disease or one of the lymphomas. In addition, he had some generalized adenopathy and a large, firm, rubbery lymph node in the right femoral region, 5 cm. in diameter. He was hospitalized because of a third-nerve paralysis with ptosis of the lid. The ophthalmologists believed that there was probably an infiltrate in the notch where the third nerve runs into the orbit. He has improved so rapidly that very little remains to be seen. My first impression was Hodgkin's disease or lymphosarcoma.

DR. E. W. NETHERTON: Histologically there was an infiltrate along the nerve fibers. Occasionally we see infiltrate completely surrounding the nerves, which might account for the paralysis.

DR. H. Z. LUND: There was a definite infiltrate around the nerves in that area. I should like to ask what the prognosis is, both the ultimate prognosis and the prognosis for this lesion, for my own information. I have seen so many of these bizarre lymphosarcomas of the lymphocytic type pursue such a long course; I wonder if that is the general trend.

DR. H. H. JOHNSON: I believe that, in general, the course is much more rapid than in Hodgkin's disease, although there is a great deal of variability. Does anyone know the answer to that?

DR. GEORGE H. CURTIS: Is this the type of growth which becomes irradiation-resistant?

DR. H. H. JOHNSON: Yes.

DR. H. N. COLE: Once in a while we see a patient with this condition who lives a surprisingly long time.

DR. H. H. JOHNSON: The reason I suggested Hodgkin's disease was that the local involvement was not as striking as that shown by many of the lymphosarcomas. In some of the cases with striking local involvement surgical removal is extremely worth while, and the patients live for some time.

DR. J. R. DRIVER: Dr. Lund has seen a section from a patient who had an isolated lesion of lymphosarcoma on the scalp. This woman was first seen about five years ago and has been seen regularly about every six months since that time. It apparently was an isolated lesion on the scalp.

Dr. Cole and I saw a patient 15 years ago with a lymphosarcoma on her scalp; she was followed for years after excision, and to my knowledge there has been no further spread. We had another patient with lesions similar to these and a generalized process. She has had a great deal of irradiation from time to time. The process has been going on now for six or seven years, and she is apparently in excellent health at present. I think, therefore, that these cases can go on for a long time, as long as 10 or 15 years, even though they may be what is apparently a generalized involvement. I do not think presence of this process necessarily means that the patient will live for only two or three years.

DR. H. H. JOHNSON: I think we have to be careful about cases of lymphocytoma, or so-called Spiegler-Fendt sarcoid. Loveman presented a paper a year ago which pointed out that the course is benign and that this growth may be indistinguishable from lymphosarcoma histologically. I should like to hear from Dr. Lund about the various types of lymphomas, i. e., follicular lymphomas.

DR. H. Z. LUND: The pathological appearance may not give a tip-off to the clinical diagnosis. Usually we see regional lymphosarcomas, sometimes in very bizarre locations. I recall one of Dr. Lenhart's cases in which the first tumor observed was a lymphosarcoma in the belly of the triceps muscle. This case has followed a fairly benign course. The growth was a small-cell lymphosarcoma. I think these peculiarly localized types tend to be the lymphocytic variety of lymphosarcoma. In the intestine we see localized lymphosarcomas, often of this lymphocytic type. On the other hand, we will see a widespread involvement of the lymph nodes with exactly the same picture follow a more rapid course to death. In the follicular lymphomas there is generally involvement of nodes. As a rule, they are not the bizarre localized type, and, even though they may be widespread, the involvement may be very slight. Lymphomas of the Hodgkin's group tend to progress more slowly.

DR. G. H. CURTIS: I wonder if it would be too far amiss to speculate on the prognosis in this case. This reaction seems to involve the nerve; that is to say, it surrounds the nerve. The patient has paresis of the eye, which suggests a periorbital involvement. I wonder if one of these lesions could suddenly appear within the skull and cause death as a brain tumor surrounding some nerve within the skull.

DR. H. Z. LUND: I expect such involvement would be extradural. We infrequently see lymphosarcomas in the brain, but it is true that extradural but still intracranial tumors might occur.

Generalized Sarcoidosis. Presented by Dr. H. H. Bremers, Dr. C. George, and Dr. C. Sunit, for the Department of Medicine, University Hospitals.

M. A., a 29-year-old Negro woman, complains of joint and muscle pains, occasional attacks of fever and chills, and weight loss during the last five months.

On examination, the pulse rate was 104 per minute. A soft precordial systolic murmur and generalized muscle tenderness were noted; these were the only positive signs elicited on admission. The skin, mucous membranes, hair and nails were normal in appearance. Three days following admission the patient displayed a few small shotty, erythematous, tender nodules on the right hand and a number of sharply defined, shiny, flat nodules over the left knee and right elbow. Microscopic sections from lesions over the knee were pathognomonic of sarcoidosis. During the first month she showed a weight loss of 11 lb. (5 kg.).

Roentgenograms of the chest taken in October and repeated in November, 1951, disclosed a uniform picture of right paratracheal nodes and hilar lymphadenopathy consistent with sarcoidosis.

The urinalysis revealed no abnormality. The hemogram showed 4,710,000 red blood cells and 7,000 white blood cells. The differential count was normal. The hemoglobin concentration was 13.5 gm. per 100 cc. The tuberculin test was negative in first and second strengths. Serum proteins were 6.9 gm. per 100 cc., with 3.5 gm. of albumin and 3.4 gm. of globulin. The albumin-globulin ratio was 1.

Histologic examination of a skin and muscle biopsy specimen was reported by Dr. H. Z. Lund as follows:

"In the cutis there are foci of lymphocytes about capillaries. There is pericapillary histiocytic proliferation. These have dense round or ovoid nuclei with moderately basophilic cytoplasm. There is a small focus of necrosis within this. Some of these cells resemble plasma cells. There are occasional neutrophiles. In the skeletal muscle there is infiltration of similar cells, notably perivascular. Among them are a few larger cells with acidophilic cytoplasm. There are granulomas of large epithelioid cells and giant cells closely resembling a sarcoid nodule. Deeper sections show a few clusters of epithelioid cells in the subcutaneous tissue."

The patient was given a 14-day course of corticotropin (ACTH), 20 mg. in 500 cc. of 5% dextrose solution in water daily by slow intravenous drip. The clinical response was striking. The fever abated; the skin lesions involuted, and the patient had a sense of well-being. There were no untoward side-effects. This treatment, however, did not have any beneficial effect on the muscular tenderness or joint pains.

Sarcoidosis with Uveitis and Blindness. Presented by Dr. H. H. Bremers, Dr. C. George, and Dr. C. Sunit, for Dr. H. N. Cole and Dr. J. R. Driver.

O. T., a Negro man aged 26, was hospitalized six months ago because of acute uveitis with rapid progressive loss of vision. Three weeks prior to that admission he noted injection of the eye and photophobia. He also noted lumps on the back of the neck and in the groin and a chronic, nonproductive cough. At the time of admission, his vision was limited to light perception. There were numerous subcutaneous nodules on the arms and forearms, a papulosquamous eruption on the lower legs, and an acneiform eruption on the face. The cervical and inguinal nodes were prominent. The tonsils were hypertrophied, and the spleen was palpable. Roentgenograms revealed disseminated infiltration of both lung fields and enlargement of mediastinal lymph nodes, consistent with sarcoidosis. There was reversal of the albumin-globulin ratio. The hemogram and urinalysis gave normal results. Microscopic sections of both skin lesions and enlarged lymph nodes showed a picture consistent with sarcoidosis.

The patient was treated with cortisone, 1:4 solution in distilled water, to both eyes every two hours during the day and atropine sulfate, 1% drops, to both eyes three times a day. After three weeks of this treatment, his vision improved from light perception to 6/60 bilaterally. He was then given a course of 20 mg. of corticotropin in 1,000 cc. of 5% dextrose solution in water intravenously daily for 16 consecutive days. The nodules in the skin disappeared; the acneiform eruption of the face became worse, and the papulosquamous eruption remained the same. Repeat roentgenograms of the chest revealed no essential change in the appearance of the lung fields, and repeat biopsies of the lymph nodes still revealed a picture consistent with

sarcoidosis. The patient was discharged on July 6, 1951. On Sept. 19, 1951, it was noted that the patient had many new lesions on the arms, legs, and chest similar to those now present. Microscopic sections of a skin biopsy specimen showed slight focal chronic dermatitis. A repeat chest roentgenogram revealed no essential change in the lung fields.

On Oct. 24, 1951, he was readmitted to the hospital in the Opthalmologic Service, as his vision had suddenly become much worse again (light perception only), although he was still using cortisone and atropine drops. He was given 15,000,000 units of killed typhoid bacilli on Oct. 25. Shortly after this lobar pneumonia developed. He was transferred to the Medical Service and was given a course of penicillin and later aureomycin. Palpable cords were noted along the medial aspects of both thighs, and it was thought that the patient might have had a pulmonary embolus. On Nov. 15, 1951, the patient had severe pain and tender swelling in the left inguinal area. He received heparin and penicillin.

On present examination, there are numerous small, erythematous, scaly papules on the arms and trunk. There are also lesions on the face and a papulosquamous eruption on the legs.

The urinalysis and hemogram showed no abnormality. The serum protein was 9.1 gm. per 100 cc., with an albumin-globin ratio of 0:5. A blood serologic test was negative. Skin tests with first-strength and second-strength purified protein derivative were now negative. Recent chest roentgenograms still revealed widespread evidence of infiltration in both lung fields.

Recent microscopic sections of skin from both the arm and the leg showed similar lesions. There were discrete masses of epithelioid cells in the upper corium. The overlying epidermis was atrophic and showed slight hyperkeratosis. There were a few lymphocytes and a rare polymorphonuclear leucocyte around the periphery of the pseudotubercles. There was an occasional Langhans-type giant cell. There was no caseous necrosis. Stains for acid-fast bacteria were negative.

DISCUSSION ON PRECEDING TWO CASES

DR. G. M. STROUD: I have previously seen two cases in which the question of a possible coexistence of tuberculosis and sarcoidosis occurred. The first case was reported by Harold and Hollister. The second case was reported by Small (*J. A. M. A.* **147**:932, 1951).

DR. H. Z. LUND: The case with muscle involvement was presented at the Tumor Clinic. At that time everyone seemed to think it was unusual to have widespread muscle involvement in sarcoidosis. There was an article on that subject by Spencer and Warren (*Arch. Int. Med.* **62**:285, 1938), in which cases of generalized Boeck's sarcoidosis were reviewed.

DR. G. A. DE OREO: It might be well, particularly in the first case, to do some electrocardiographic studies, particularly in view of the pains that this patient is having. Some of them might mask angioid types of pain, which I think are present. A recent article in *The Journal of the American Medical Association* showed that these lesions may develop in the musculature of the heart as well, producing bundle block.

DR. H. H. BREMERS: She has had electrocardiographic studies, and I do not believe that they suggested any significant change.

DR. E. W. NETHERTON: I hesitate to suggest therapy in this case, but we showed cases before this society a year or so ago of sarcoidosis in identical twins. One of them had uveitis and that, together with the lung changes, cleared entirely with calciferol therapy. Her sister did not tolerate the treatment well and is now complaining of pain in the lumbar muscles and the muscles of her chest, which I interpreted as being myositis. In view of what Dr. Lund has said, I believe that we should do a muscle biopsy. If we did more muscle biopsies in these cases, we would find more lesions. It is not a common practice to do muscle biopsies in cases of sarcoidosis, unless there are specific symptoms referable to the muscles.

Dermatitis Herpetiformis. Presented by DR. H. H. BREMERS, DR. C. GEORGE, and DR. C. SUNIT, for DR. H. N. COLE and DR. J. R. DRIVER.

F. R., a white man aged 57, has had a generalized pruritus for nine months.

Physical examination reveals excoriated erythematous papules on the legs, thighs, trunk, and arms and pigmented areas over the back. The hands and feet are somewhat cyanotic

and cold. The results of examination otherwise are normal, except that both the dorsalis pedis and the right posterior tibial arterial pulsations are not palpable.

The hemoglobin concentration was 13.6 gm. per 100 cc., and there were 5,180,000 red blood cells per cubic millimeter. There were 13,100 white blood cells, with 67% polymorphonuclear leucocytes, 13% lymphocytes, 15% eosinophiles, 4% monocytes, and 1% basophiles. The urinalysis revealed nothing abnormal. The blood urea nitrogen was 10.5 mg. per 100 cc. The serum protein was 6.6 gm. per 100 cc., with an albumin-globulin ratio of 1.1. A blood serologic test was negative. A skin test with second-strength purified protein derivative was positive. The sputum was negative for acid-fast bacteria. Chest roentgenograms showed no abnormality.

Microscopic sections of a skin biopsy specimen from the left suprascapular area taken in May, 1951, showed a small ulcer extending through the epidermis. It was covered with serous exudate, containing many polymorphonuclear leucocytes and occasional eosinophiles. Similar cells were seen at the base. There was proliferation of the capillary endothelium. The cells were large and basophilic. About the ulcer there were perivascular infiltration of polymorphonuclear leucocytes, eosinophiles and lymphocytes and proliferation of histiocytes.

A section obtained from a repeat biopsy specimen taken on Nov. 21, 1951, showed an ulcer which may represent an ulcerated vesicle, for there was undermining at the edges and exudation of polymorphonuclear leucocytes. At the base and in the corium lateral to this there were infiltration of eosinophiles and proliferation of histiocytes.

The pruritus has become less with administration of 400 mg. of nicotinic acid per day orally in divided doses. There was some response to local therapy but none to use of benzyl benzoate emulsion. There was no response to diphenhydramine (benadryl®) or tripelennamine (pyribenzamine®) given orally. Priscoline® (2-benzyl-2-imidazoline) hydrochloride, 50 mg. three times a day, was administered orally with some relief of the coldness of the extremities.

DISCUSSION

DR. H. H. BREMERS: I have nothing to comment on except that the histologic picture is characteristic of dermatitis herpetiformis (Duhring's disease). The patient has not responded too favorably to treatment. Use of potassium arsenite solution (Fowler's solution) has just been started.

DR. H. N. COLE: Is he a psychiatric patient?

DR. H. H. BREMERS: He was seen by members of the Peripheral Vascular Service, and they thought that he had generalized arteriosclerosis. That apparently is the explanation for the changes in the extremities. He had a stellate block while in the hospital, and little response was obtained in one extremity. We used priscoline® without much benefit.

DR. G. A. DE OREO: The lesions present on this man's ears are rather common in dermatitis herpetiformis. I can recall two cases in which lesions were on the ears for a number of years before they appeared anywhere else on the body.

DR. E. W. HALLINGER: Did this patient receive sulfapyridine?

DR. H. H. BREMERS: No, he did not.

DR. F. M. MCDONALD, Akron: I should like to substantiate the remarks of Dr. De Oreo regarding the distribution of the lesions on the ears. I have seen that several times, and I do not believe much mention has been made of it. I also wondered why this man has not been given sulfapyridine.

Xeroderma Pigmentosum. Presented by DR. H. N. COLE, DR. J. R. DRIVER, and DR. H. N. COLE JR.

R. G., a white woman aged 33, was first seen on May 4, 1923. There was a history that she had had a great increase in freckles on the face. She had a brother aged 13, and there was another brother, aged 2 years, both living and well and having no difficulty. The father and mother are first cousins.

The patient has been under observation off and on through the years and has had many areas of malignant change, which have been treated with endothermy, curettage, and implanta-

tion of radium-platinum needles at the base of the tumors. At one time she had extensive involvement of a node in front of the left ear, which was treated by interstitial irradiation, and a remarkable result was achieved.

The patient has endeavored to stay out of the sunlight, going out only in the early morning and in the late afternoon. She also has used sun-preventive preparations.

Today she has a very extensive, deep freckling over the face, over the backs of the hands, and on the exposed parts. However, this freckling extends down only to the upper portion of her breast and upper part of her chest anteriorly and posteriorly. The covered parts are almost entirely free from any pigmentation, showing the influence of radiation in the causation of the trouble. There are scars over the face in areas where the tumors have been removed in the past, but the condition is apparently quiescent, and she has had nothing that required treatment for some years.

Several biopsy specimens have been taken, the microscopic descriptions of which are reported as follows:

1. "There are hyperpigmentation of the epidermis, intercellular and intracellular edema, and melanocytes in the upper cutis. There is slight lymphocytic and histiocytic infiltration. No basophilic degeneration is seen. In a few places there is marked hyperplasia of the basal cells. The diagnosis is hyperpigmentation of skin, resembling lentigo and atypical hyperplasia of basal epithelium."

2. "There is a peculiar proliferation of basal cells in a stratum at the base of the epidermis. The cells have certain characteristics of prickle cells. Prickles are demonstrable in some, but the cytoplasm is scant. There is much intercellular and extracellular edema. Mitoses are numerous. Deep in the cutis is an invasive, well-differentiated squamous-cell carcinoma. The diagnosis is intraepidermal basal-cell carcinoma and (invasive) well differentiated squamous-cell carcinoma."

3. "There is marked overgrowth of squamous epithelium, retaining, however, a fairly orderly pattern. There is individual cell keratinization. Mitotic figures are scanty. There is hyperkeratosis. The diagnosis is hyperkeratosis and acanthosis."

4. "There is an invasive tumor tending to have a lobular pattern. The cells are fusiform or stellate. There is much intercellular edema. There are foci of squamoid transition and keratin formation. There is moderate peripheral palisading. In the adjacent epidermis there is moderate hyperplasia. The basal cells have clear-cut prickles, and there is intercellular edema. The diagnosis is basal-cell carcinoma."

DISCUSSION

DR. J. A. GAMMEL: I think I saw this patient five years ago. I want to congratulate DR. COLE and DR. DRIVER for keeping her alive so long.

DR. H. H. JOHNSON: I saw her first 13 years ago, and my impression is that she is very much better than she was at that time. She is tending to form keratin at a markedly reduced rate. I think it is remarkable that she is doing so much better as an adult than as an adolescent and young woman.

DR. J. R. DRIVER: As many of you know, Dr. Cole and I have followed this patient since she was a very small child, about 3 years old. For a long time we had a great deal of trouble with her. She had many lesions on her face. One on the left forehead was treated with interstitial implantation of radium needles. At the same time she had metastases to the preauricular node on that side, which were treated by interstitial irradiation.

DR. H. N. COLE: The remarkable thing about this case is that below the nipples there is some pigmentation, but not too much. From there down there is practically no pigmentation. The patient has been told to go outdoors only in the early morning and in the late afternoon and has always worn a hat. I think that that has had a great deal to do with the fact that she has lived as long as she has. I have not checked the literature, but I imagine that she is really one of the oldest living patients with xeroderma pigmentosum who has had as extensive a process as she has.

DR. H. Z. LUND: I do not know how rare xeroderma pigmentosum is, but to see such an excellent example of the various types of lesions is unusual. The pigmented areas look like

ordinary ephelides. And then in some of these areas there are superficial types of basal-cell epithelioma which clinically appear to be lentigines. There is still another type which is definitely basal-cell epithelioma, and then there is the prickle-cell epithelioma.

Cutaneous Horns and Neurosyphilis. Presented by DR. H. H. BREMERS, DR. C. GEORGE, and DR. C. SUNIT, for DR. H. N. COLE and DR. J. R. DRIVER.

Multiple Basal-Cell Epitheliomata. Presented by DR. MELVIN BRODY.

Parapsoriasis en Plaques. Presented by DR. H. N. COLE, DR. J. R. DRIVER, and DR. H. N. COLE JR.

Paresis Accentuated by Surgery. Presented by DR. H. H. BREMERS, DR. C. GEORGE, and DR. C. SUNIT, for the Psychiatric Department, University Hospitals.

METROPOLITAN DERMATOLOGICAL SOCIETY OF LOS ANGELES

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March 25, 1952

Case for Therapeutic Recommendations: Mycosis Fungoides. Presented by DR. WALTER S. GREEN and DR. LAURENCE J. UNDERWOOD.

C. C. L. is a 74-year-old white man who has had erythematous, scaly plaques densely distributed over his trunk and extremities for more than 20 years. During the past five years the plaques have increased in number and size. Many becoming indurated and lesions also developing on the face and neck. Itching has been minimal until the past year.

Roentgen therapy (approximately 2 erythema doses) was given in 1949 by radiologists to the trunk and extremities.

Biopsy specimens taken in 1948, 1950, and 1952 have been interpreted microscopically to be consistent with mycosis fungoides. Blood cell counts have been normal except for a recent monocytosis (15%).

Microscopic-section and kodachrome® photographs are presented with the case.

Mycosis Fungoides. Presented by DR. DONALD ROSMAN.

O. N. is an 81-year-old white man who is retired. Family history reveals that the patient's father had "skin trouble," but it disappeared later in life. Past history indicates that the patient had a rash on his face about eight years ago, which disappeared after application of a salve.

The present eruption began in December, 1951, on the sacrum and left leg. It gradually spread to involve the greater part of his body. The eruption is extremely itchy, especially in the evening. His drug intake consisted of psyllium hydrophilic mucilloid with dextrose (metamucil®), "one-a-day" vitamins (a multivitamin preparation), and digitalis.

Physical examination reveals a well-developed, well-nourished, healthy-looking elderly white man. Over his trunk and extremities, especially the lower extremities, the patient has many discrete macular patches of dermatitis. Some are eczematous and covered with a crust. Other patches on his sacrum and thighs look velvety-red and feel infiltrated. His teeth reveal some marginal decay.

Laboratory studies show a normal blood cell count and a negative blood Wassermann reaction.

A biopsy specimen is described as follows: The epidermis is atrophic and is invaded by edema and cellular elements. In some areas, microscopic vesicles are formed. In other areas, colliquative degeneration of the cells of the epidermis suggests vesiculation, but the cells do not reach that stage of degeneration. Also invading the epidermis are large monocytes, around which are clear degenerated zones. Also in the cutis there is a slight infiltrate which is observed perivascularly and consists essentially of a polymorphous cellular infiltrate. The diagnosis is premycotic mycosis fungoides (Dr. L. H. Winer).

The patient has been treated with fractional doses of x-ray irradiation.

DISCUSSION ON PRECEDING TWO CASES

DR. STANTON B. MAY: The first case struck me as being of mycosis fungoides as presented. I believe, probably, that the second case, that presented by Dr. Rosman, is one of the same disease. I would have a little more doubt about the latter patient's diagnosis, as I have seen

that type of lesion get well, and I am afraid such a label may lead us to do nothing for this man. The patches, of course, appear as nummular eczema in a rather unusual location. I should like to state that I have a few reservations in spite of the report of the pathologist and the many features that go along with that diagnosis pathologically. I would go ahead and treat it; it may be possible to allay the pruritus, and the dermatitis may clear up.

DR. EDWARD L. MURPHY: In regard to the first case, I believe that the duration of this condition and the scaling that is present on the back would lead me to entertain a very simple diagnosis of psoriasis. The second patient tells us that at one time, early in the disease, he had penile lesions. I, therefore, believe that the eruption fits into the diagnosis of Sulzberger-Garb dermatitis better than into any other.

DR. LAURENCE J. UNDERWOOD: The second patient presented evidence of sensitization dermatitis on the extremities, and I thought, clinically, it was on the basis of an autoeczematization process, rather than mycosis fungoides.

DR. DONALD ROSMAN: When I first saw this man (second patient), my impressions were that he had a drug eruption or possible dermatitis herpetiformis (Duhring's disease). At that time the dermatitis was much more extensive and was much different from its present appearance. X-ray therapy has certainly changed the appearance. Prior to the x-ray therapy, I prescribed sulfapyridine for three weeks, and, if anything, he got worse. I questioned him carefully concerning his drug intake, since the possibility of a dermatitis medicamentosa was one of my first impressions. All he had been taking was digitalis and psyllium hydrophilic mucilloid with dextrose. He stopped taking these but with no apparent effect on the eruption. He was given many different kinds of local medication but all without effect. Finally, a biopsy specimen was taken and reported as showing mycosis fungoides. This is the best diagnosis for this patient, I believe, especially since I have followed him for some time.

Case for Therapeutic Suggestions: Chronic Discoid Lupus Erythematosus of Scalp?
Presented by DR. MEYER BERKE.

L. M. is a 42-year-old white housewife. Onset of present illness occurred about two years ago with erythematosus scaling plaques on the scalp and resultant persistent alopecia. She had a small erythematous plaque on the left posterior ear lobe which was "burned" off two years ago. New plaques have appeared and enlarge with central alopecia. Recently a small, erythematous, scaly, circinate lesion has appeared on the posterior surface of the right ear lobe.

Examination reveals several variably sized erythematous scaling oval to round plaques in the scalp. In the center of the right ear lobe there is a small circinate scaling erythematous lesion approximately 0.5 cm. in diameter.

On laboratory study the serologic tests for syphilis gave negative reactions. Results of routine urinalysis and the differential blood cell count were normal. Culture for fungi showed no growth. The red blood cell count was 3,970,000; the white blood cell count 5,100, the hemoglobin content, 81% (12.5 gm. per 100 cc.). The color index was 1.0.

Biopsy report indicates that the epidermis is markedly thinned and atrophic with mild hyperkeratosis and plugging of follicles. There are marked atrophy of the hair follicles and sebaceous glands and an increased density of the collagen with homogenization. A mild perivascular infiltrate of chronic inflammatory cells is present.

No treatment has been prescribed, although in the past the scalp lesions have been treated as alopecia areata.

Pernio. Presented by DR. DONALD ROSMAN.

C. W. E. is a 34-year-old white housewife who has a past history of acne. Her toes were frostbitten about 22 years ago. When her feet get cold, they turn grayish-white, but never blue, and they feel numb. About four years ago, she noticed that her big toes began hurting her, especially on elevation. About one year ago, she noted an eruption on her big toes, and then, one month ago, it spread to her other toes. Pressure on her toes makes it worse. She says that she feels cold most of the time.

On the tip of her left big toe, the patient has several pinhead-sized erythematous papules. She has one smaller lesion on the left fourth toe. Several of her toes are dusky-red. The dorsalis pedis pulsations are good.

The red blood cell count, white blood cell count, and plasma iodine are essentially normal.

Biopsy report indicates that these sections of skin present mainly hyperkeratosis, acanthosis, and a banal infiltrate in the upper corium. The granular layer is somewhat thickened, and there is some vacuolation of the cells in the prickle-cell layer. The blood vessels in the upper cutis are dilated and surrounded by an infiltrate which consists mostly of small lymphocytes and an occasional epithelioid cell.

Treatment has consisted of ichthammol "ichthyol" ointment and nicotinamide, 50 mg. three times a day.

Case for Diagnosis: Lupus Erythematosus? Presented by DR. IRVING A. LEWE and (by invitation) DR. AARON WILLIAMSON.

B. F., a 24-year-old white woman, was first seen by one of us (A. W.) in July, 1951, with an erythematous eruption covering the cutaneous surfaces of the upper lip and an erythematopapular eruption on the dorsa of the forearms. The eruption had appeared shortly before her visit. She also complained of dryness and scaliness of the vermilion surface of the lips. A biopsy specimen taken from the forearm was reported histologically by Dr. Wilbert Sachs, of New York, to show the following:

"Through the upper cutis are basophilic degeneration and edema. The superficial vessels are dilated. There is a focal cellular reaction about the vessels and somewhat about the adnexa. The epidermis is thin and flattened; the follicles are dilated and plugged. The elastic tissue is somewhat fragmented but does not show too much change.

"NOTE.—Although the picture is suggestive of lupus erythematosus, the elastic tissue findings are not. This is more probably an actinic dermatitis or may be an early stage of lupus erythematosus."

A sun-protective cream, 5% preparation of menthyl anthranilate and titanium dioxide in vanishing cream base ("a-fil"), was prescribed, and the eruption finally subsided in November, 1951. The present eruption began in December, 1951. It first appeared as an itching rash on the right palm and soon spread to the dorsa of the fingers. A biopsy specimen taken from the dorsum of the left ring finger was described by Dr. Wilbert Sachs as follows:

"The epidermis is acanthotic and somewhat flattened. The granular and horny layers are considerably increased. For the most part the palisade layer is washed out. Throughout the upper cutis there is an intense infiltration of small round and wandering connective tissue cells. The blood vessels are dilated, and there is edema, especially in the subepidermic region. There is no basophilic degeneration, and the elastic tissue shows no characteristic features. We are unable to make a diagnosis of lupus erythematosus from these sections."

The microscopic diagnosis was "possibility of lichen planus."

Since moving to California from New York, the patient stated that she has been subject to a "prickly-heat-like rash" on areas of the skin exposed to the sun, except for a period from the age of 13 to 17 during which time she went to the beach frequently and had no eruption. There is no history of her taking drugs, and she stated that her general health is good except for nervousness and headaches.

Examination of the skin revealed a patchy, erythematous eruption on the dorsa of the fingers of the left hand, mainly just below the nail folds. There was scaling of several finger tips, and on the right palm were several pea-sized, erythematous macules. Examination of the mouth revealed a well-defined, triangular, whitish, reticulated plaque on the left buccal mucosa, just posterior to the angle of the mouth, and a whitish line or lesion on the mucosal surface of the left upper lip.

The patient received three weekly intramuscular injections of bismuth subsalicylate in oil, but a severe local reaction developed, so its use was discontinued. Two superficial x-ray treatments of 75 r each were then administered to the affected areas on the hands, the last on Jan. 15, 1952. The itching subsided, and the eruption showed definite improvement following this treatment but began to flare up again a few weeks ago. She has been using "quotane" (1-[β-dimethylaminoethoxy]-3-*n*-butylisoquinoline monohydrochloride) lotion during the past two weeks to relieve the intense pruritus.

DISCUSSION ON PRECEDING THREE CASES

DR. ERNEST T. FOX: In the case presented by Dr. Berke, since focal infection is known to be an important factor in the production or continuance of some forms of lupus erythematosus, it seems only reasonable that the tonsils of this patient should be examined further to determine whether infection is present and, if so, to what degree. I observed that the tonsils were enlarged, that the anterior and posterior tonsillar pillars were injected, and that considerable cheesy and semiliquid materials were present in the crypts. In addition, the patient previously lived in a cold climate where, in general, tonsils more frequently are enlarged and harbor a higher percentage of virulent bacteria than do those in persons who live in more temperate environments.

In the case presented by Dr. Lewe and Dr. Williamson, the woman was observed to have what is called an acrocyanotic type of circulation in all the extremities. The hands and feet were moist, somewhat livid or violaceous. It is suggested that her use of tobacco be greatly restricted or eliminated because nicotine and other noxious chemicals in tobacco smoke cause contraction of the smooth muscle fibers of the arterioles and thus may reduce further her already inadequate circulation.

DR. STANTON B. MAY: In regard to the first case, in my experience, the treatment of lupus erythematosus of the scalp has been particularly ineffectual. I think the patient should have a trial of gold therapy, and I should like to ask Dr. Feldman if he has had any experience with cortisone ointment. I don't think anything else offers much promise.

The case presented by Dr. Lewe and Dr. Williamson struck me as being one of fairly active lupus erythematosus that will bear close watching for possible dissemination.

In regard to Dr. Rosman's patient I wondered if anything would be gained by a blood uric acid determination because of the history of pain in the foot.

DR. LAURENCE J. UNDERWOOD: I think we are fortunate in seeing the case presented by Dr. Lewe and Dr. Williamson. It is a very interesting case and, I believe, one of lupus erythematosus. The disease may be in a predisseminating phase. Has she had laboratory examinations, including a white blood cell count, recently?

The first case was one of classic lupus erythematosus.

DR. MARGARET STORKAN: The patient described by Dr. Lewe has clinical signs and symptoms of subacute lupus erythematosus. It has been recently brought to our attention that there is an association between the incidence of neoplasm and that of lupus erythematosus. The presence of an abdominal or breast neoplasm can easily be determined, and an examination of the peripheral blood and bone marrow can easily be done; these would aid in definitive diagnosis.

DR. FRED F. FELDMAN: I don't think we can definitely make a diganosis of subacute lupus erythematosus for Dr. Lewe's patient without further laboratory study. Certainly we need a blood cell count, urinalysis, and possibly a search for the L. E. cell. The biopsy performed on the finger was interpreted as showing lichen planus. The patient has some wavy white lines on the buccal mucosa which are suggestive of lichen planus. I think the diagnosis of lupus erythematosus should be seriously considered but reserved until further study is made.

I feel that Dr. Berke's patient has classic chronic discoid lupus erythematosus. I don't think that topical use of cortisone would be of value in this case as the lesions are atrophic. I think that others will bear out my conviction that the tumid type of lesion responds the best to cortisone ointment, whereas little can be expected in atrophic plaques.

DR. HERBERT A. FISHBEIN: Recognizing that lupus erythematosus is a disease of collagenous tissue, as therapy I suggest the use of acetylsalicylic acid and paraaminobenzoic acid (PABA), and, regarding Dr. Rosman's case, I should like to suggest methantheline (banthine®) bromide as adjunctive therapy.

DR. HAROLD C. FISHMAN: I should like to suggest in Dr. Lewe's case the diagnosis of chilblain and lupus of Hutchinson, a form of lupus erythematosus. I think this is a classic case and extremely rare. We are very fortunate to see it. Because this case fits the classical description of Hutchinson, I think we should have a report on it.

DR. IRVING A. LEWE: I first want to thank the discussers for their diagnostic and therapeutic suggestions, and I will try to carry out as many of them as possible. I have considered the various diagnoses mentioned in the discussion, but my personal feeling is that this is lupus erythematosus, probably of the subacute disseminated type.

The patient's blood cell count was reported as being normal, and this, along with the fact that she has had no systemic symptoms since the onset of the eruption last July, is a little against the condition's being a disseminated form of lupus erythematosus. However, further laboratory work, including a sedimentation rate and a search for L. E. cells, will be done.

Multiple Basal-Cell Epitheliomata and Paraffinoma. Presented by Dr. Fred F. Feldman.

J. T. is a 70-year-old white woman. The reliability and accuracy of the history are not established because of the patient's apparent mental retardation. She states that at the age of 12 years a paralysis of the right side of her face developed which has persisted to date. About 40 years ago a physician injected wax under the skin of her cheeks for cosmetic reasons. About 20 years ago the lesion in the mid-portion of her forehead first developed and never became larger than its present size. In recent years she had similar reddish nodules on her temples, nose, and cheeks. She states that the linear scar on the right side of her nose is the result of an operation performed because of a "cyst" of her right lower eyelid. No history of biopsy or past treatment for the skin lesions was obtained.

There is a dime-sized reddish-blue nodule with irregular borders on the mid-forehead. There is an elevated, flat-topped, infiltrated, circumscribed, slightly larger bluish-red nodule on the right side of the nose. Similar but smaller lesions appear on the left upper temporal region and the left lower outer eyelid. A biopsy specimen was taken from a tumor of the right temple; the tissue was found to be very friable. There are large, firm, movable subcutaneous masses occupying almost the entire cheek on the left and the lower part of the right cheek.

The pathologist reported the microscopic examination of the biopsy specimen taken from the lesion of the right temple to show the following:

"The piece of skin is covered by a thinned-out epidermis. The corium has been replaced by large irregular compact masses of oval cells. The peripheral layer is well defined and consists of columnar cells arranged perpendicular to the surrounding stroma. Mitoses are infrequent. There is an occasional small pool of eosin-stained material which may represent keratin. The surrounding connective tissue trabeculae are well vascularized.

"On one edge of this piece of skin there are two foreign bodies, possibly calcified. The adjoining stroma shows inflammatory reaction."

The microscopic diagnosis was "basal-cell carcinoma."

Case for Therapeutic Recommendations: Steatocystoma Multiplex. Presented by Dr. Laurence J. Underwood and Dr. Walter S. Green.

Mrs. D. C., a 30-year-old white woman, has had numerous asymptomatic cystic nodules 1 to 8 mm. in diameter distributed predominantly along the mid-line of the abdomen and chest. The lesions have been present 10 years. The color is that of the overlying skin or slightly yellowish.

Histopathologically the condition is consistent with steatocystoma multiplex.

DISCUSSION ON PRECEDING TWO CASES

Dr. Ernest T. Fox: In my opinion Dr. Feldman's patient should have each of the multiple basal-cell carcinomata treated by curettage and desiccation.

In regard to the case presented by Dr. Underwood and Dr. Green, several months ago I observed a man with the same clinical picture as that presented by this patient, with, in addition, many similar lesions on his back. It was a laborious task, but each of those lesions was treated individually by incision, expression of the contents, and phenolization of the cavity. The scar tissue was not noticeable, and the results were good.

Dr. John W. Walters: In the cases of steatocystoma that I have seen, the lesions are more yellowish than they are in this woman. Dr. Fox stated that incising each of the lesions would be helpful. In my cases this produced very good results.

Dr. Harold Price: I should like to point out that in the paraffinoma, if the substance injected was a paraffin, we are actually dealing with a hydrocarbon and not a fat. Fatty acids, esters, and cholesterol are not present in the paraffin substances. I can't reconcile the injection of a paraffin wax substance with the development of a xanthomatous type of lesion.

DR. FRED F. FELDMAN: This patient was not concerned about the paraffinoma but only about the lesion in the middle of the forehead. She has basal-cell epitheliomata, some of which are as old as 20 years, and yet the largest lesion does not exceed 2 cm. in diameter. This is another example of the relatively benign nature of many basal-cell epitheliomata.

Psoriasis Nummularis Precipitated by Recurrent Erythema Multiforme Iris (?). Presented by DR. JOHN W. WALTERS.

V. O. is a 24-year-old white housewife. Family history reveals no psoriasis. The patient has a history of a skin rash on the body starting five years ago. The first attack was of three week's duration, with a recurrence six months later, repeating itself again in six months. She then remained free of lesions for a year, but since then recurrences have been every three months. She states that there were lesions in the mouth occurring only when she had an exacerbation. There also were lesions on the palms and soles. During her first pregnancy she had one attack which cleared before delivery. She was seen in August, 1950, by a dermatologist who made a diagnosis of a rather typical erythema multiforme iris, and she was treated with antihistamines. Aureomycin hydrochloride was advised but was not taken. I saw her first in March, 1951, at which time she had an extensive erythema multiforme iris. There was some bullous formation in several of the lesions but no isolated bullae. Some areas were crusted and impetiginous. These were treated with bacitracin. Her teeth had been checked, and no foci of infection were found. There was a vaginal discharge, and gynecological consultation was advised. She did not return for further therapy.

She was seen today for the first time since March, 1951. The patient stated she has had the condition since then with no remissions, but the lesions have changed in appearance. The lesions also developed in the scalp. She complains of much pruritus.

The areas in the scalp resemble psoriasis with typical scaling. On the body there are various-sized circinate erythematous lesions; they are most extensive on the arms and legs. There are no bullae and no typical iris lesions as seen previously. On the legs there are areas that also resemble psoriasis. There are no lesions in the mouth.

The results of complete blood cell count, urinalysis, and cervical smear are essentially normal. The urine is negative for porphyrins.

Erythema Multiforme Bullosum (?); Disseminated Herpes Simplex (?). Presented by DR. LEONARD E. SAVITT.

J. C. is a 26-year-old white man and a graduate student in anthropology. He had mumps in 1943.

For the past three years he has had recurrent eruption of the arms, back, hips, and mouth every three or four months which clears spontaneously in about one month. He is helped little by treatment. The patient believes the eruption started with bites on the leg. He has had cold sores accompanying the eruption a few times.

Examination reveals an annular erythematous lesion of the left arm, erythema and edema of frenulum of the tongue, and scaling of right anterior leg.

Aureomycin hydrochloride expedited healing slightly, and penicillin troches helped the eruption in the mouth. A course of smallpox vaccinations is being given at present, so far by scratch technique only. The vaccinations result in lesions at the site of the scratch that simulate those of the original eruption. One large lesion occurred a few inches from the site of vaccination.

DISCUSSION ON PRECEDING TWO CASES

DR. HERBERT A. FISHBEIN: In the case presented by Dr. Walters I agree with the diagnosis. It is an interesting example of the Koebner phenomenon. In Dr. Savitt's case, I should like to present for thought the fact that during the smallpox epidemic of 1946 in New York it was not unusual to see, after the mass vaccination procedure, numerous reactions of this form of erythema multiforme.

DR. HAROLD PRICE: The second case was to me one of the most interesting of all. It brings up the controversy about whether vaccine virus inoculation is of value in the treatment of herpes simplex and erythema multiforme, diseases which are supposedly caused by viruses that

are different from cowpox virus. It would be interesting to see whether the same type of erythema-multiforme-like eruption could be induced with an inactivated cowpox virus. If such a reaction does occur with an inactivated virus, then I believe some attention should be given to the relation between the eruption and possible allergy to cow lymph.

DR. LEONARD E. SAVITT: I thank the discussers for their comments regarding the relation of erythema multiforme bullosum and herpes simplex. I have treated a few patients having erythema multiforme with smallpox injections and had no results. One of the patients thereupon went to another dermatologist, who used aureomycin hydrochloride with excellent results.

Regarding the production of lesions from the use of intradermal smallpox injections, at one time I used such a vaccination on a pemphigus patient who had been getting along fairly well for a time, but her condition went downhill soon after she was vaccinated several times. Typical lesions of pemphigus were formed at the site of inoculation. Dr. Nelson Paul Anderson advises that erythema multiforme in which herpes simplex occurs responds to treatment with repeated injections of smallpox vaccine.

DR. JOHN W. WALTERS: I presented this case because I thought it of interest to see psoriasis developing suddenly after recurrent attacks of erythema multiforme iris. This is the third case of psoriasis precipitated by some other type of skin condition that I have had in the past year. In one case, in which treatment is still being given, psoriasis followed a penicillin reaction. I first saw this patient in the hospital on consultation. She had a typical penicillin reaction on the skin, but on her knee and chest were areas of psoriasis. Biopsy revealed a true psoriasis. There was no history of psoriasis in the family, nor did she previously have psoriasis. In the second case a true psoriasis developed in a man after circumcision.

Lichen Sclerosus et Atrophicus Accompanied with Leucoplakia. Presented by DR. LEONARD E. SAVITT.

E. N. is a 29-year-old white housewife of German-Irish extraction. History reveals no cancer in family. The patient saw a physician five years ago, at which time the lesion of vulva was discovered.

The patient has no complaint regarding the present lesion. She has been treated with hormones for infantile uterus and ovaries; this therapy has not helped the lesion.

Examination reveals infantile uterus and ovaries and a white atrophic ill-defined lesion of labia majora, mostly on the right and extending onto the anus.

The first biopsy specimen taken from fissure by a gynecologist was reported by a general pathologist as showing leucoplakia. A second biopsy specimen was interpreted by the histopathologist, Dr. Louis Winer, as characteristic of lichen sclerosis et atrophicus.

Treatment has consisted of estrogens and vitamin A (by gynecologist) with no improvement. A preparation of conjugated estrogenic substances (premarin * cream), 1.25 mg. per gram, was given for two weeks.

DISCUSSION

DR. ERNEST T. FOX: Although the causes of this disease are unknown, it is of interest to me to speculate about the possible influence of traumata in relation to the onset of this disease, especially in this instance. This young woman has engaged for years in many athletic activities which included horseback riding; the involved areas have been traumatized literally hundreds of times by bruising contacts with the pommel of the saddle and frequently by severe falls. Might there not be some relation of repeated trauma to the development of the disease in this woman?

DR. STANTON B. MAY: I should like to say that clinically this didn't resemble the usual appearance of lichen sclerosus. To me this was almost like a scar in the upper vulva. I didn't agree with the diagnosis clinically, but, when I saw the slide, I agreed with the diagnosis. I have found that treatment with carbon dioxide is of some value in a case of this type.

DR. LAURENCE J. UNDERWOOD: It is my understanding that kraurosis vulvae and lichen sclerosus of the vulva present similar pathologic findings except for a thickening of the vessels which is supposedly a characteristic of kraurosis.

DR. LEONARD E. SAVITT: I feel that the most important thing in management of the patient's condition is the prognosis. I saw this patient first at a tumor board at which the consensus was to perform a vulvectomy, and my intervention rescued the patient from that.

It seems historically these lesions were probably all called kraurosis vulvae, and subsequently lichen sclerosus et atrophicus was separated from the group. Now we are beginning to feel that they are probably variants of the same entity. The particular point in this instance is the presence of leucoplakia proved historically in a case of lichen sclerosus et atrophicus. That, of course, might modify our prognosis so that careful observation will be essential.

Case for Therapeutic Suggestions: Cystic Acne Vulgaris with Subcutaneous Abscesses of Abdomen, Neck, and Shoulders. Presented by DR. STANTON B. MAY.

F. H. is a 20-year-old Mexican youth who is attending college. He was presented before this society previously, at the November, 1951, meeting.

The patient had osteomyelitis of the hip at the age of 6 years.

I first saw the patient one year ago when he came to me with a history of "boils" on the neck for the past eight months. He has been under the care of another dermatologist and myself most of this time, with fairly inadequate results. New deep abscesses keep appearing and draining for an indefinite time. Several months ago, a large abscess appeared over the epigastrium. The back, sides, and lateral inferior aspects of the neck are sites of frequent, deep, painful, slow-healing abscesses. Smaller cystic lesions occasionally appear on the face.

Chronically draining, tender, soft, cystic swellings are seen on the lateral jaws. There are previously drained swellings on the back and sides of the neck. The face is markedly scarred. The back is essentially clear.

Pus from a recent abscess revealed hemolytic Staphylococcus citreus. Another culture done in October, 1951, revealed nonhemolytic, pure Gram-positive cocci (Staphylococcus albus). Antibiotic-sensitivity tests reveal resistance to penicillin, bacitracin, streptomycin, and chloramphenicol (chloromycetin®) but marked sensitivity to aureomycin and terramycin. The blood sugar was normal. Blood cell count reveals leucocytosis.

Treatment has consisted of x-ray irradiation, Staphylococcus toxoid injections, sulfurated lime (Vleminckx's) solution packs, diethylstilbestrol, terramycin, and aureomycin given orally, penicillin injections, sulfonamide drugs given orally, autogenous vaccine injections, surgical drainage of abscesses, injections of a multivitamin and mineral salt preparation ("vi-syneral"), injection of nonspecific protein and lipoprotein preparations (activin® and omnadin®), and cortisone given orally.

Case for Therapeutic Suggestions: Recalcitrant Atopic Dermatitis of Face and Neck. Presented by DR. STANTON B. MAY.

J. B. is a 28-year-old Caucasian. His aunt and other relatives have asthma. The patient has frequent sore throats and a discharging nose.

For the past 10 years he has had eczema of face, neck, and bends of the arms and legs. He was discharged from the Navy because of this.

In appearance he is a thin, short, fairly well-developed, well-nourished white man.

The skin of the face, eyelids, and front and sides of neck, extending down onto the chest and superior shoulders, presents a thickened, erythematous, somewhat pale, rough, dry, scaly, lichenified dermatitis.

Roentgenograms of sinuses were negative for pathologic change. Numerous scratch tests were negative.

The patient has been receiving treatment for more than two years, with quick clearing of flexures but persistence of eczema on the face and neck. Only mild improvement has occurred in spite of many forms of therapy, as follows: injections of combination of histamine and despeciated horse serum globulin containing no free histamine (hapamine®); superficial x-ray irradiation; chlorcyclizine hydrochloride (perazil®) given orally; application of naphthalan-ichthammol paste and coal tar solution N. F. as cream; phenendamine tartrate (thephorin®) given orally; high-protein diet with supplement (delcos® granules); autohemotherapy; use of coparaffinate (iso-par®) and crotamiton (eurax®) ointments; hot quartz mercury vapor light; application of iodochlorhydroxyquin (vioform®) cream; fatty acid capsules and vitamin B_{12} given orally; pollen extract injections; mephenesin (tolserol®), 0.5 gm. four times a day, and glutamic acid hydrochloride given orally; use of cortisone (cortone®) ointment; calciferol

(drisdol®), 150,000 units per day, and procaine-ascorbic acid capsules given orally; application of chlorcyclizine hydrochloride cream; intravenous injections of a pure carbohydrate derivative from certain bacteria (pyromen®); administration of vitamin A, 100,000 units per day, and use of an ointment preparation containing crude coal tar, zinc oxide, and starch (supertah®). The last drug was of some help.

DISCUSSION ON PRECEDING TWO CASES

DR. CHARLES SHERTER: I saw a similar case of cystic acne when I was in training. Assuming that massive antibiotic therapy, staphylococci injections, and the other usual procedures are tried, the patient should be placed in the hands of a plastic surgeon for excision of the involved area and grafting. It was found that cystic acne was common among our troops in the tropics, and the nicest form of therapy consisted of excision of the unhealthy tissue and subsequent grafting.

DR. ERNEST T. FOX: I should like to point out that this patient with cystic acne obviously is maladjusted, particularly in the sexual sphere. Recently he has been engaged to or had an alleged personal alliance with a certain young lady. Despite this supposedly close association, he denies any sexual relation in recent months. Further inquiry revealed that in past years he has had at least one homosexual experience, although he stated that such practices were not common with him. The conscious and unconscious conflicts in this sphere may well be one of the factors responsible for his recalcitrant and long-continued eruption.

I want to compliment Dr. May on his wide range of therapeutic efforts. Although he cultured several pathogenic organisms from the lesions, he did not mention whether these cultures were used to make a specific or autogenous vaccine. Further leading questions of more than academic interest are the following: 1. Have roentgenograms of the chest been done? 2. Have guinea-pig inoculations been performed to aid in the discovery of acid-fast organisms? 3. Have any other evidences of tuberculous infection been uncovered?

DR. JOHN W. WALTERS: During the war, in the Marianna Islands, I saw many cases of severe cystic acne. Dr. Sherter remarked about the radical surgical procedure and skin grafting. At first, because of conditions little surgery could be done. However, later more of this type of treatment was accomplished, but new cystic areas continued to develop. I used all treatment available at the time with little result.

I was wondering if Dr. May used these antibiotics long enough. I feel that in these severe cases one should use antibiotics over a long period, i. e., for at least three months, reducing the dosage as indicated.

DR. STANTON B. MAY: In the case of cystic acne, Dr. Walters pointed out that I may not have persisted with the antibiotic therapy. That point is very well taken. I have reviewed the situation in my own mind, and that is the criticism I had of my conduct of the case. I feel that there is something systemically wrong, and there seems to be no resistance to the infection. I have thought of excising the area. The patient exhibited a very deep, large abscess on the epigastrium, and I incised it twice and drained it.

In regard to the case of atopic dermatitis, I am wondering about the value of psychogenic therapy, and I believe that not much is going to be gained by further medical treatment. Possibly I should look a little beneath the surface for some emotional factor that is keeping this infection going. A week or two ago the patient felt somewhat better after he had broken off with his last girl friend.

NOTE.—May 9, 1952, the patient has considerably improved after intravenous typhoid vaccine therapy.

Case for Diagnosis: Duhring's Disease (Dermatitis Herpetiformis)? Impetigo Herpetiformis? Moniliids? Presented by DR. JOHN W. CARNEY.

R. M. is a 41-year-old Negro nurse. Family history and past history are noncontributory.

History of present illness reveals onset about Christmas, 1951, of a pruritic, pustular dermatitis involving the nape of the neck; subsequently, new lesions continued to appear at intervals to involve other parts of the body. Mild fever was noted at the onset of the eruption. The patient, on her own, applied methylrosaniline chloride (gentian violet) and sulfathiazole ointment.

Physical examination shows a well-developed woman appearing neither acutely nor chronically ill.

Dermatologically there are pinhead- to split-pea-sized dry pustular lesions involving the nape of the neck, the breasts, the axillae, the pubic region, and sparsely the legs and arms. Some of the lesions are confluent and some discrete. A few of the lesions on the legs and arms are thin-walled vesicles or vesicopustules on a noninflammatory base. All the lesions have a tendency toward grouping.

Laboratory studies on Jan. 21, 1952, revealed no abnormality on urinalysis, a negative serologic reaction for syphilis, and a normal blood sugar content.

On March 21, wet mounts from bleb and from vaginal exudate were negative for Candida (Monilia), and there has been no growth to date from the culture. On March 22, urinalysis gave normal results. Complete blood cell count was normal except for 3,800,000 red cells; vaginal smear was negative for Neisseria gonorrheae and for Trichomonas organisms.

Biopsy shows a subcorneal vesicle containing polymorphonuclear leucocytes, with an occasional eosinophile, and minimal to moderate acanthosis. The upper third of the cutis shows edema and dilatation of the blood vessels and mild, nonspecific cellular reaction in upper and middle thirds of the cutis.

Treatment consisted of administration of 1,800,000 units of penicillin intramuscularly, chloramphenicol (chloromycetin®) cream locally, aureomycin ointment locally, and sulfapyridine orally for six days. There was no noticeable benefit from any of the mentioned medications. Repeated spraying of house with insecticides was of no benefit.

DISCUSSION

Dr. Leonard E. Savitt: I feel that this is an instance of impetigo herpetiformis. This case doesn't follow the typical characteristics; only one typical case has been presented in this area in the past several years. Dr. Ayres and I reported a similar case that we felt resembled impetigo herpetiformis and was probably a variant of a disseminated herpes simplex. At that time, in the preaureomycin days, I was successful in treating the patient with repeated doses of smallpox vaccine, which gave a specific and dramatic response. Since then, supposedly aureomycin has been found to be effective.

Dr. Harold Price: I was able to see this patient with Dr. Carney at one time, and I feel that probably this condition represents hypersensitivity in a person who somehow or other acquired a skin infection in a soil which probably is immunologically defenseless. I suggest that a sugar-tolerance test be done, that antibiotics be given locally, and that treatment with aureomycin be continued, along with frequent antiseptic soap washes.

Dr. Stanton B. May: I don't profess to know what this patient's condition is. Histologically, the vesicle is quite superficial favoring an impetiginous type of lesion. My impression is that dermatitis herptiformis would be more deeply placed in the epidermis. My best impression is that this is some type of pyodermic lesion. Because of the annularity of the neck lesions, I think that further tests should be made to rule out any mycotic factor.

Dr. Irving A. Lewe: I should like to ask Dr. Carney if an attempt has been made to look for foci of infection.

Dr. John W. Carney: The interesting feature, and perhaps a significant one, in this case is the changing nature of the lesions. The most impressive change, three weeks ago, was the appearance of dewdrop-like vesicles on the skin; the bases were nonerythematous. The dermatitis of the neck, in contrast to that present tonight, consisted merely of a few vesicles. Two weeks ago the breasts and pubic areas presented hyperpigmented, flattened pustules, each having a centrally adherent crust, and all the lesions were grouped to form a circinate border. It is evident that there has been considerable change from the situation just described. I might add that the pyoderma of the neck has not responded to antibiotics administered parenterally or locally.

Attention was directed to the genital area because the patient stated that at about the time of the onset of her eruption, she noiced a very foul vaginal discharge. The possibility of a moniliasis with monilids was investigated and subsequently ruled out.

I feel that the clinical appearance and changing nature of the dermatitis is in keeping with impetigo herpetiformis; however, the patient's excellent health and nonpregnant state are

against this diagnosis and, to me, point toward dermatitis herpetiformis. The patient is rather independent and will take medicine as she desires and not as directed; consequently, I do not know whether her condition is clearing because of the sulfapyridine or because of some other medication.

I want to express my appreciation to the discussers for their diagnostic and therapeutic suggestions.

Hemangioma of the Face (Nevus Flammeus or Capillary Type) (?). Presented by Dr. Stanton B. May.

The patient is a 2½-year-old boy with a light pinkness of the chin and sides of jaws, fairly deeply placed in the skin, which has been present since birth and persists essentially unchanged.

Carbon dioxide slush applied Feb. 27 resulted in no change. The mother feels there has been some lightening of the lesion after solid carbon dioxide was applied March 12, 1952.

DISCUSSION

Dr. John W. Walters: In a certain light, there seemed to be small raised lines in this lesion, and I thought there might be some keloid formation. The mother told me that she noticed these raised lines, which were not present before treatment. They may have resulted from the use of carbon dioxide.

Dr. Charles Sherter: My impressions are that thorium X would be least valuable in treatment of an infiltrative lesion because the radiation effect is almost wholly epidermal. In a recent article in *The Journal of Investigative Dermatology*, thorium X-impregnated skin was applied to photographic emulsion plates, and it was found that ionization was almost completely localized in the epidermis.

My point is that mature capillaries in the corium will be unaffected by the very weak and superficial alpha-ray effect of thorium X.

Radium plaque therapy or grenz-ray therapy might prove helpful.

Dr. Harold Price: That, of course, may solve the problem as to why there is deeper penetration. I am sure that there is some penetration through the epidermis along the follicles so that some of the thorium X is lodged in the cutis.

Dr. Fred F. Feldman: Dr. Bucky, of New York, feels that he can improve a large percentage of patients with nevus flammeus by the use of grenz rays. He feels that he can cause a lesion to fade to the same extent that an area can be lightened by diascopy.

Dr. Harold C. Fishman: I should like to add one comment. We are all agreed that nothing except thorium X benefits nevus flammeus, and, contrary to popular opinion, there must be more than alpha-radiation. Definite changes in the basal-cell layers are of such magnitude that I am sure thorium goes into the dermis.

Dr Stanton B. May: From the practical standpoint it seems to me that it would be best to discontinue treatment and let this patient alone, and I propose to do that.

Obituaries

RICHARD L. SUTTON, M.D.
1878-1952

Dr. Richard L. Sutton Sr., dermatologist, writer, big game hunter, and fisherman, died May 18 from a major coronary occlusion secondary to an operation two days before for repair of a diaphragmatic hernia. It was the sixth major operation he had undergone within the past two years. Thus ends the career of one of the most colorful men in American dermatology.

Dr. Sutton was born July 9, 1878, the son of a minister, and studied at the University of Missouri. He took his medical degree at the University Medical College, Kansas City, in 1901, and did additional work at George Washington University, United States Naval Medical School, Johns Hopkins University, and later, took courses in London, Hamburg, with Paul G. Unna, Berlin, Vienna, and Paris. He was an assistant surgeon in the U. S. Navy (retired) and for a long time "Head" of the Department of Dermatology at the University of Kansas Medical School and Visiting Dermatologist to the University Hospital.

He had received honorary degrees from the University of Missouri and Washburn University and was a life member of the Royal Geographical Society of London, a member of the French Geographical Society, a corresponding member of the British Dermatological Society, a Fellow of The Royal Society, Edinburgh, and a member of The Explorers Club, of the American Polar Society, and of many anglers' clubs in Australia and New Zealand.

As a dermatologist, Dr. Sutton was particularly known for his large book, "Diseases of the Skin" (St. Louis, C. V. Mosby Company), which has gone through ten editions. The book has been very widely used in medical schools and by physicians and students not only on the American continent but also abroad—particularly in England. He also published a smaller edition, and in later years both of these were published in collaboration with his son, Dr. Richard L. Sutton Jr. In addition, he had published many articles on his specialty from time to time.

But for an energetic character like Dick Sutton, the practice of his specialty, the conduct of his classes in medical school, and early hospital rounds at 7 a. m. were not enough. His restless spirit simply could not be confined. He loved to fish, and this meant not just bass and trout fishing, but tarpon fishing in Texas, Mexico, and Florida; sail fishing in the Gulf Stream; frequent trips to Wisconsin and Lake of the Woods for muskellunge, and even trips to the West Coast of South America, New Zealand, and Australia for marlin and sharks.

As a hunter, he loved "chicken" shooting in western Kansas and Nebraska and turkey shooting in the Southwest. However, his big spirit had to wander farther afield, and only a safari to East Africa for leopards, rhinos, buffalo, hippopatami, etc., would satisfy him. Moreover, he and his son shot tigers in Indo-China, which almost cost him his life from estivoautumnal malaria. He even made a trip to the Arctic, a birthday gift to his daughter, for polar bears, walrus, musk oxen, and seal.

These various excursions brought forth "An African Holiday," "Tiger Trails in Southern Asia," "An Arctic Safari," "Around the World with Camera and Rifle," "Silver Kings of Aransas Pass," "Chapter Headings and Other Verse, " etc. Moreover, his articles on fishing, hunting, and travel were constantly coming forth in this and that sporting magazine. He dearly loved tarpon fishing at Aransas Pass, Texas, and at Tampico, Mexico. His collection of guns was something to behold and admire, and he gave bountifully to the museums at the University of

RICHARD L. SUTTON, M.D.
1878-1952

(From a painting in the library of the University of Kansas School of Medicine.)

Missouri and at Kansas City tusks, rhino heads, zebra skins, blowguns, etc., as well as live polar bears, zebras, kangaroos, musk oxen, seals, monkeys, and other unusual animals.

Dr. Sutton loved poetry and wrote much of it. I received from him many years ago the following little verses which have been preserved and which make a fitting close to the passing of this many-sided friend and physician:

SUNSET AT BIMINI

We shall spend a day on the quiet bay
Where the little sail boats ride,
Near the mangrove trees and the sunken keys
Where the ghostlike bone fish hide.

When the sun goes down at Alice Town,
Sinks low in the Western Sea,
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R. L. S.—'34

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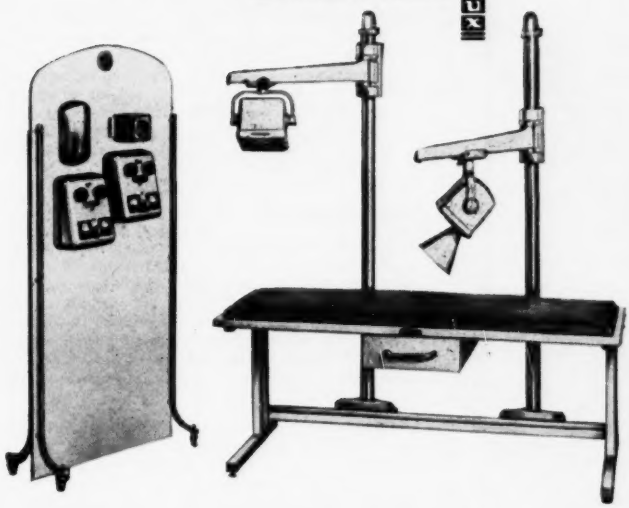

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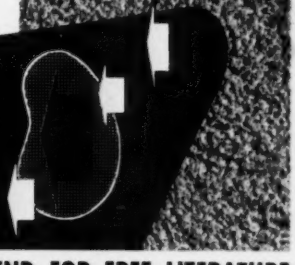

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* Lane, C. G., "Therapeutic Dermatitis", New Eng. J. Med., 246:77-81, 1952

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☐ Mar-O-Oil Regular Shampoo
☐ Mar-O-Oil Super Foamy Shampoo

*Name*_____, *M.D.*

*Address*_____

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Pleasingly and efficiently
serving patient and physician
during all seasons

SUPERFATTED

BASIS* SOAP

*Trade mark

For dry sensitive skin

Available at Prescription Pharmacies

DUKE LABORATORIES, INC
STAMFORD CONN U S A

Mfgrs. of Aquaphor—Elastoplast, Trade marks

For patients requiring hand protection—

Waterproof, CLOTH-LINED RUBBER GLOVES

Excellent protection where *dishwashing, laundering, cleaning, dusting, painting, gardening, etc.*, may cause dermatitis or intensify skin disorders.

Soft *cotton-lining* absorbs perspiration, prevents contact with rubber, makes gloves slip on and off easily.

Easy to work in, light and pliable. Long cuffs protect wrists. Women *like* wearing them!

For women: Small, medium and large sizes.

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$9 a dozen pairs, $1.25 a pair postpaid

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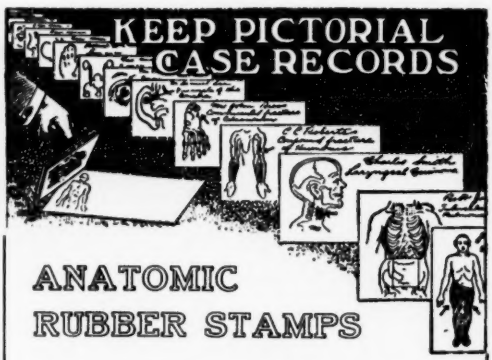

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Use BARTON'S Rubber Stamp Outlines on History Charts.

Make a few notations on a stamped impression and you have an accurate graphic record of examinations.

Send for FREE Folder illustrating sample outlines

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Rubber Stamp Makers since 1885

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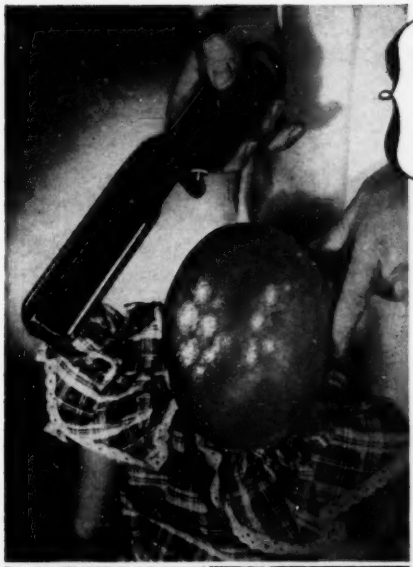

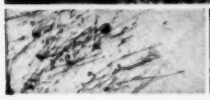

UNDER NORMAL LIGHT

UNDER MINERALIGHT SL 3660

for use in the diagnosis of TINEA CAPITIS

ACCEPTED COUNCIL ON PHYSICAL MEDICINE AND REHABILITATION AMERICAN MEDICAL ASSOCIATION

a powerful new instrument the MINERALITE long wave ultra-violet diagnostic lamp

Lightweight, compact, easy to handle, the Mineralight SL 3660 starts instantly. No warm up or cooling off period as required by similar lamps. Emitting energy in the general 3660 Angstrom band (unlike 2537AU), this lamp does not cause erythema, and so is considered non-injurious. The lamp fluoresces many substances which are not activated intensely by shorter wave ultra-violet (2537AU). The SL 3660 radiates at a wave length and intensity of special value to the dermatologist in recognizing hairs infected with microsporum lanosum and M. audouini.

For additional information, write for bulletin D.S. "New ultra-violet generator for use in the diagnosis of Tinea Capitis by Fluorescence" by J. Walter Wilson, M.D., Los Angeles... Reprinted from the A.M.A. Archives of Dermatology and Syphilology June 1951. Vol. 63. pp. 771 and 772. Copyright. 1951. by American Medical Association.

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MANUFACTURERS OF ULTRA-VIOLET EQUIPMENT SINCE 1932

RETAIL PRICE $1.00 BOTTLE 6 OZ.

FORMULA

Myristic and lauric acids saponified with polyamine alkali to a low pH(8), with neutralized polycarboxylic acid, enriched with lanolin esters, given extraordinary solvency with propylene glycol.

Vegetable or mineral tars may be added in desired percentage.

Removes ointments and medications gently but thoroughly.

High foaming, extremely economical in use, tolerated by scalps which shed epithelium from overstrong detergents.

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.....M.D.

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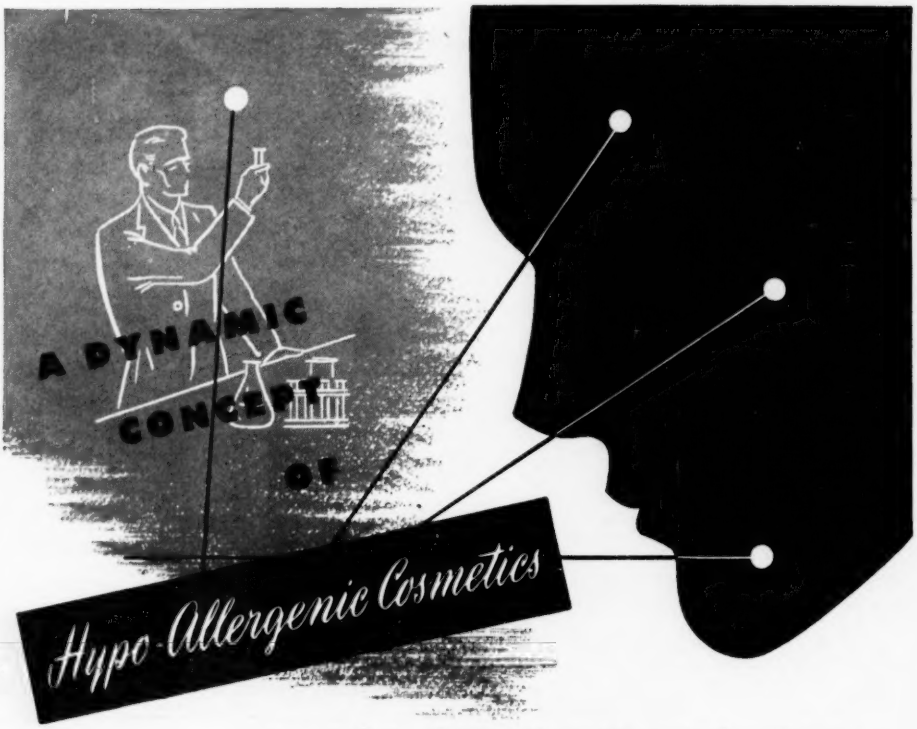

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Materials used in Marcelle Hypo-Allergenic Cosmetics are under continuous scrutiny. Literature on cosmetic allergy is carefully evaluated and frequent clinical studies are made. Patch testing with raw materials and finished products is a routine procedure. Marcelle consultation service on individual cases of cosmetic sensitivity is at the disposal of doctors everywhere.

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MARCELLE COSMETICS, INC.
1741 NORTH WESTERN AVENUE, CHICAGO 47, ILLINOIS

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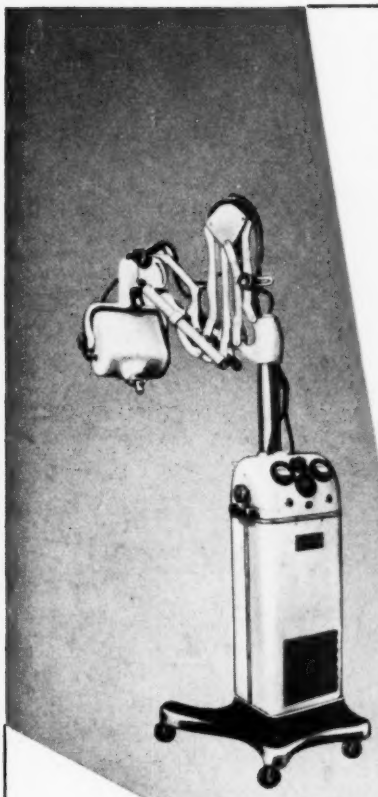

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XRM Model G-3 Bucky Therapy Apparatus (as illustrated). Completely mobile, minimum space requirements. No installation of any type required.

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